UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PAMLAB, L.L.C., METABOLITE LABORATORIES, INC., and BRECKENRIDGE PHARMACEUTICAL, INC.,	Civil Action No. 10 CV 7680
Plaintiffs,	
v.	JURY TRIAL DEMANDED
SETON PHARMACEUTICALS, L.L.C.,	
Defendant.	

COMPLAINT

Plaintiffs Pamlab, L.L.C., Metabolite Laboratories, Inc., and Breckenridge Pharmaceutical, Inc., by and through their attorneys, state as follows for their Complaint against Defendant Seton Pharmaceuticals, L.L.C.:

The Parties

1. Plaintiff Pamlab, L.L.C. ("Pamlab") is a limited liability company existing under the laws of the State of Louisiana, with its principal place of business at 4099 Highway 190, Covington, Louisiana, 70433.

2. Plaintiff Metabolite Laboratories, Inc. ("Metabolite") is a corporation existing under the laws of the State of Colorado, with its principal place of business at 301 Garfield Street, Unit 2-West, Denver, Colorado, 80206.

3. Breckenridge Pharmaceutical, Inc. ("Breckenridge") is a corporation existing under the laws of the State of Florida, with its principal place of business at 1141 South Rogers Circle, Suite 3, Boca Raton, Florida, 33487.

4. Defendant Seton Pharmaceuticals, L.L.C. ("Seton") is a New Jersey limited liability company with its principal place of business at the Atlantic Corporate Center, 2317 Highway 34, Suite 1E, Manasquan, New Jersey, 08736.

Jurisdiction And Venue

5. This Court has original jurisdiction over the subject matter of this lawsuit under 28 U.S.C. §§ 1331 and 1338(a), because it arises under the patent laws of the United States, as well as under 28 U.S.C. § 1331 and 15 U.S.C. § 1221(a), because it concerns violations of section 43 of the Lanham Act, 15 U.S.C. § 1125.

6. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1400 and 1391. On information and belief, Seton is subject to personal jurisdiction in this district because it markets and sells products to nationwide retail drug store chains, including those with locations within this judicial district, as well as through nationwide distributors and databases that target this judicial district.

STATEMENT OF FACTS

The Research Leading to the Patent in Suit and Pamlab's Patent License

7. Homocysteine is an amino acid and a natural byproduct of the human body's conversion of methionine into cysteine. If a body lacks the enzyme necessary to complete that conversion, or if the body lacks vitamins such as folic acid, B_6 and B_{12}, the concentration of homocysteine in the blood and urine increases.

8. In recent years, researchers have identified an increased homocysteine level in the blood (hyperhomocysteinemia) as an additional and independent risk factor for arteriosclerosis and coronary heart diseases. Similarly, hyperhomocysteinemia is linked with repeatedly occurring venous thromboses and apoplexy strokes.

9. Studies have shown that a combination of vitamins B_6, B_{12}, and folic acid can lower homocysteine levels in most patients. Thus, doctors increasingly recommend that their patients with elevated homocysteine levels take supplements of vitamin B_6, vitamin B_{12}, and especially folic acid.

10. Several years ago, Plaintiff Pamlab noted the medical interest in treating elevated homocysteine levels with vitamin B_{12}, vitamin B_6, and folic acid (also known as folate), and decided to formulate a product having these vitamins in suitable quantities. During the development of this product, Pamlab discovered the groundbreaking work of two hematology professors at the University of Colorado School of Medicine, Dr. Robert H. Allen and Dr. Sally P. Stabler.

11. Drs. Allen and Stabler have devoted their careers to studying vitamin B_{12}, vitamin B_6, and folate. Their clinical work has been at the forefront of the research examining the relationship between those vitamins and homocysteine. Their studies have been widely cited and published in prestigious scientific journals such as the New England Journal of Medicine, and they have also been awarded a number of United States patents.

12. Among these is United States Patent No. 6,528,496, entitled "Compositions treating, preventing, or reducing elevated metabolic levels" ("the '496 Patent"), which was duly and legally issued to Drs. Allen and Stabler on March 4, 2003. The '496 Patent is attached as Exhibit A.

13. Dr. Allen formed Plaintiff Metabolite under the University of Colorado's guidelines. The patents and applications leading to the '496 Patent, and later the '496 Patent itself, were assigned to Metabolite, so that Metabolite is the owner of all right, title, and interest in the '496 Patent, as well as the related patents.

14. Accordingly, Pamlab approached Metabolite in 1999 and began discussions concerning a patent license for certain products. Pamlab first launched the product at issue (as discussed hereinafter) in the fall of 1999, while these discussions were in progress. Then on January 11, 2000, Pamlab entered into a license agreement with Metabolite (the "Patent License"), under which Metabolite granted Pamlab an exclusive license to certain formulations under several related patents and applications (one of which, through a subsequent continuation application, issued as the '496 Patent). Moreover, under the Patent License (as amended), Pamlab has the right to enforce the '496 Patent.

Pamlab's Licensed Product Foltx®

15. Pursuant to the Patent License, Pamlab manufactures and sells a product with the trademarked name of "Foltx®." Pamlab pays Metabolite a royalty based on the value of the sales of Foltx®.

16. Foltx® is marketed to licensed physicians and other healthcare professionals.

17. Foltx® contains three active ingredients, namely vitamin B_{12}, vitamin B_6, and folic acid. When Foltx® was first marketed by Pamlab in October, 1999, it contained 1 mg. of vitamin B_{12}, 25 mg. of vitamin B_6, and 2.5 mg. of folic acid (the "1 mg. Foltx®"). Beginning in June, 2004, Pamlab introduced Foltx® containing 2 mg. of vitamin B_{12} instead of 1 mg. (the "2 mg. Foltx®"), and discontinued sales of the 1 mg. Foltx®.

18. After Pamlab launched Foltx® in October, 1999, the market for this product grew steadily as physicians increasingly recognized the relationship between elevated homocysteine and vitamin B_{12}, vitamin B_6, and folate.

19. Much of this recognition is attributable to the huge investment in education that Pamlab has undertaken. Pamlab has spent millions of dollars calling on tens of thousands of physicians through Pamlab's sales force, providing millions of product samples, publishing articles and advertisements in medical journals, and funding additional clinical studies.

20. Pamlab markets Foltx® to physicians as a medical food product intended for the specific dietary management of individuals under a physician's treatment for hyperhomocysteinemia, with particular emphasis on individuals with or at risk for atherosclerotic vascular disease in the coronary, peripheral, or cerebral vessels, or individuals with vitamin B_{12} deficiency.

Breckenridge's Patent Sublicense and Its Licensed Folic Acid Products

21. In 2007, Breckenridge entered into a patent sublicense with Pamlab under a number of the Metabolite patents, with the express consent of Metabolite.

22. Under the patent sublicense, Breckenridge now markets the only licensed generic versions of both the 1 mg. Foltx® and the 2 mg. Foltx®. Breckenridge markets a product containing 1 mg. of vitamin B_{12}, 25 mg. of vitamin B_6, and 2.5 mg. of folic acid as "Folbee®", and a product containing 2 mg. of vitamin B_{12} 25 mg. of vitamin B_6, and 2.5 mg. of folic acid as "Folbic™".

23. Breckenridge pays a royalty to Pamlab pursuant to the sublicense, which in turn pays a royalty to Metabolite.

Seton's Folic Acid Product

24. Upon information and belief, Seton has had manufactured, for sale in the United States, a product which Seton represents to contain 2 mg. of vitamin B_{12}, 25 mg. of vitamin B_6, and 2.5 mg. folic acid ("Seton's Folic Acid Product"), the same active ingredients as 2 mg. Foltx® and Folbic™.

25. Upon information and belief, Seton has offered, or intends in the near future to offer, Seton's Folic Acid Product for sale in commerce in the United States.

26. Upon information and belief, in offering its Folic Acid Product for sale, Seton has represented or will represent, explicitly or implicitly, that its Folic Acid Product is substitutable for Foltx® and/or Folbic™.

27. Upon information and belief, Seton has not scientifically determined whether its Folic Acid Product is substitutable for Foltx® and/or Folbic™.

COUNT I
Patent Infringement

28. Plaintiffs incorporate the allegations of the preceding paragraphs as though fully set forth herein.

29. By manufacturing, selling, and/or offering to sell its Folic Acid Product, Seton has infringed and continues to infringe the '496 Patent under 35 U.S.C. section 271(a), and/or by having its Folic Acid Product manufactured to contain the active ingredients as specified above, with both knowledge and intent that its Folic Acid Product would infringe the '496 Patent, Seton has induced infringement of and/or contributed to the infringement of the '496 Patent under 35 U.S.C. section 271 (b) and/or (c).

30. Plaintiffs have been injured thereby, in an amount to be determined at trial.

31. Upon information and belief, the infringement of the '496 Patent by Seton is willful.

32. Upon information and belief, Seton will continue its infringement of the '496 Patent unless its acts infringement are restrained and enjoined by this Court. Should Seton be permitted to continue its acts of infringement of the '496 Patent, Plaintiffs will suffer irreparable injury for which they have no adequate remedy at law.

COUNT II
Violation Of The Lanham Act

33. Plaintiffs incorporate the allegations of the preceding paragraphs as though fully set forth herein.

34. In the alternative, if Seton's Folic Acid Product does not infringe the '496 Patent, then Seton has misrepresented, or intends to misrepresent, the active ingredients contained in this product, which constitutes false and/or misleading descriptions and representations of fact that misrepresent the nature, characteristics, and/or qualities of Seton's Folic Acid Product, and otherwise constitutes false advertising under section 43(a) of the Lanham Act, 15 U.S.C. § 1125(a).

35. In addition, upon information and belief, because Seton has not scientifically determined whether Seton's Folic Acid Product is substitutable for Foltx® and/or Folbic™, the explicit or implied representations by Seton, in commerce, that its Folic Acid Product is substitutable for Foltx® and/or Folbic™ are false and/or misleading descriptions and representations of fact that misrepresent the nature, characteristics, and/or qualities of Seton's Folic Acid Product, and otherwise constitute false advertising in violation of section 43(a) of the Lanham Act, 15 U.S.C. § 1125(a).

36. Plaintiffs have been and/or will be injured thereby, in an amount to be determined at trial.

37. Upon information and belief, Seton will continue its violation of the Lanham Act unless such violations thereof are restrained and enjoined by this Court. Should Seton be permitted to continue its false and misleading descriptions and representations of fact and false advertising, Plaintiffs will suffer irreparable injury for which they have no adequate remedy at law.

WHEREFORE, Plaintiffs request that the Court:

(a) Preliminarily and permanently enjoin Seton, its officers, directors, employees, partners, agents, licensees, servants, successors and assigns, and any and all persons acting in privity or concert with them, from making, having made, using, offering to sell, or selling Seton's Folic Acid Product;

(b) Enter judgment against Seton for compensatory damages by reason of its infringement of the '496 Patent, as determined at trial, but not less than a reasonable royalty, in an amount to be determined at trial;

(c) Determine that such infringement was willful, and award treble damages to Plaintiffs by reason thereof;

(d) Declare this case to be "exceptional" within the meaning of 35 U.S.C. § 285, entitling Plaintiffs to an award of their reasonable attorneys fees, expenses and costs of this action;

(e) Preliminarily and permanently enjoin Seton, its officers, directors, employees, partners, agents, licensees, servants, successors and assigns, and any and all persons acting in

privity or concert with them, from representing that Seton's Folic Acid Product is substitutable for Foltx® and/or Folbic™;

(f) Enter judgment against Seton for compensatory damages by reason of its violation of the Lanham Act, as determined at trial, in an amount to be determined at trial; and

(g) Enter an Order granting Plaintiffs such other and additional relief against Seton as may be just and proper in the circumstances.

DEMAND FOR TRIAL BY JURY

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Plaintiffs demand a trial by jury of all issues properly triable to a jury in this case.

Dated: October 7, 2010

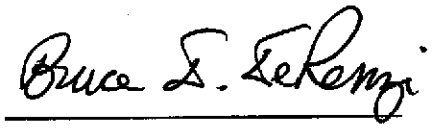

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EXHIBIT A

US006528496B1

(12) **United States Patent**
Allen et al.

(10) **Patent No.: US 6,528,496 B1**
(45) **Date of Patent: Mar. 4, 2003**

(54) **COMPOSITIONS TREATING, PREVENTING OR REDUCING ELEVATED METABOLIC LEVELS**

(76) Inventors: **Robert H. Allen**, 301 Garfield St., Unit 2-West, Denver, CO (US) 80206; **Sally P. Stabler**, 641 Milwaukee St., Denver, CO (US) 80206

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/793,214**

(22) Filed: **Feb. 26, 2001**

Related U.S. Application Data

(60) Continuation of application No. 09/273,754, filed on Mar. 22, 1999, now Pat. No. 6,297,224, which is a continuation of application No. 09/012,955, filed on Jan. 26, 1998, now Pat. No. 6,207,651, which is a continuation of application No. 08/693,515, filed on Aug. 2, 1996, now Pat. No. 5,795,873, which is a division of application No. 07/999,499, filed on Dec. 29, 1992, now Pat. No. 5,563,126.

(51) Int. Cl.[7] **A01N 43/04**; A01N 43/58; A01N 43/60; A01N 43/40; A61K 31/70; A61K 31/495; A61K 31/50; A61K 31/44

(52) U.S. Cl. **514/52**; 514/249; 514/345

(58) Field of Search 514/52, 249, 345, 514/251, 276, 335, 474, 563, 642, 745; 424/439, 557, 558, 643; 536/26.4; 435/88; 426/648

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(List continued on next page.)

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Assistant Examiner—Zachariah Lucas
(74) *Attorney, Agent, or Firm*—Gibson, Dunn & Crutcher LLP

(57) **ABSTRACT**

A method for orally administering vitamin preparations is described which combine vitamin B_{12} (B_{12}, cobalamin) and folic acid (folate), with and without pyridoxine (B_6), for preventing and treating elevated serum homocysteine (HC), cystathionine (CT), methylmalonic acid (MMA), or 2-methylcitric acid (2-MCA) levels. These metabolites have been shown to be indicative of B_{12} and/or folic acid deficiencies. Further, it is likely that a B_6 deficiency may be present with a B_{12} or folate deficiency. The method of the invention is also for use in lowering serum HC, CT, MMA, or 2-MCA in patients with or at risk for neuropsychiatric, vascular, renal or hematologic diseases. The method of the present invention eliminates the costly and time consuming steps of distinguishing between vitamin deficiencies once a deficiency is found by measurement of serum metabolite levels. The present invention is of particular benefit to the populations at risk for elevated serum metabolite levels, such as the people over the age of 65, and populations that have or are at risk for neuropsychiatric, vascular, renal and hematologic diseases.

11 Claims, 11 Drawing Sheets

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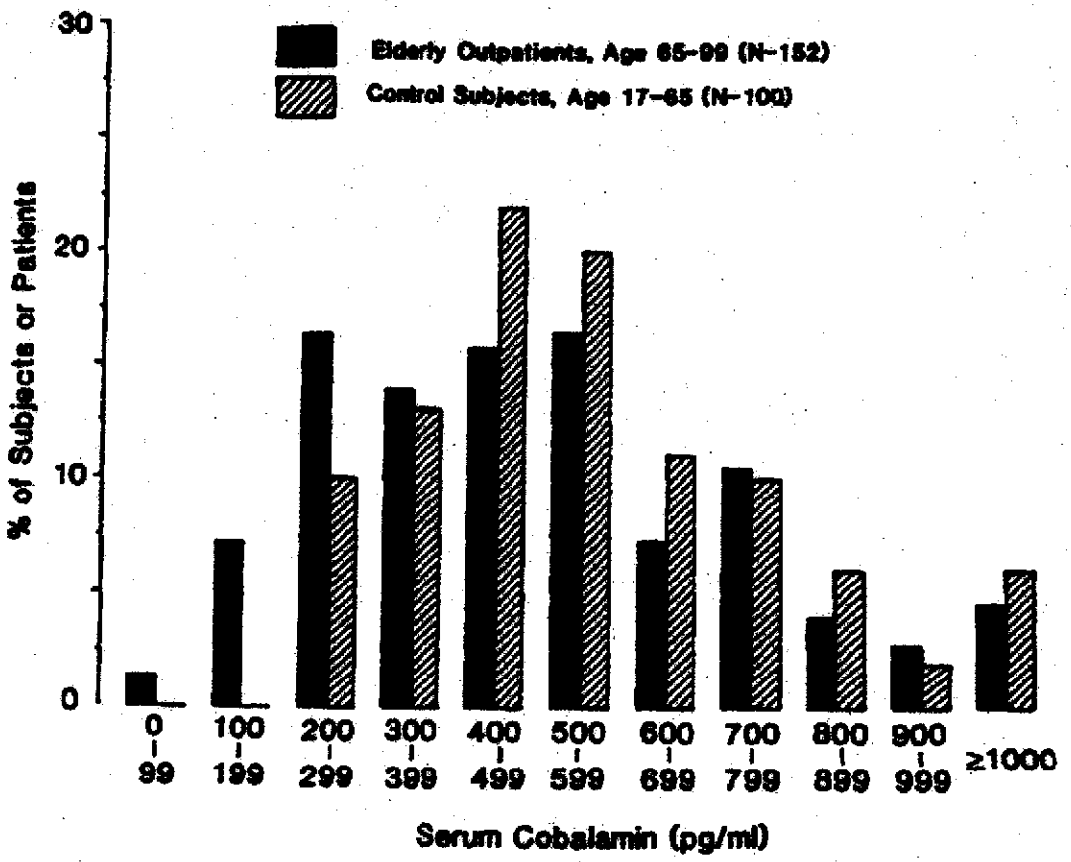
Elderly Outpatients, Age 65-99 (N=152)
Control Subjects, Age 17-65 (N=100)
% of Subjects or Patients
30
20
10
0
0 99
100 199
200 299
300 399
400 499
500 599
600 699
700 799
800 899
900 999
≥1000
Serum Cobalamin (pg/ml)

FIGURE 1

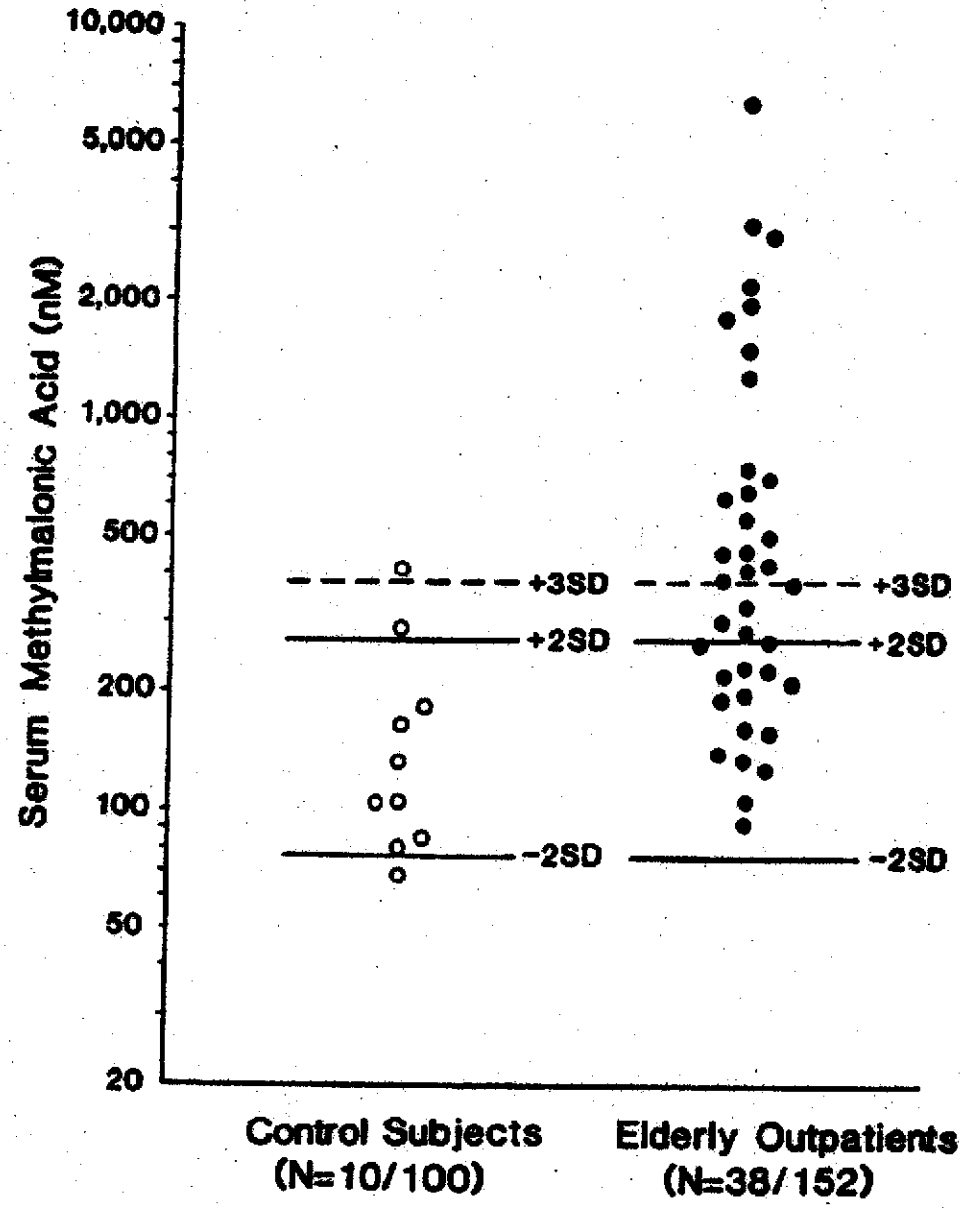
10,000
5,000
2,000
1,000
500
200
100
50
20
Serum Methylmalonic Acid (nM)
+3SD
+2SD
-2SD
+3SD
+2SD
-2SD
Control Subjects
(N=10/100)
Elderly Outpatients
(N=38/152)

FIGURE 2

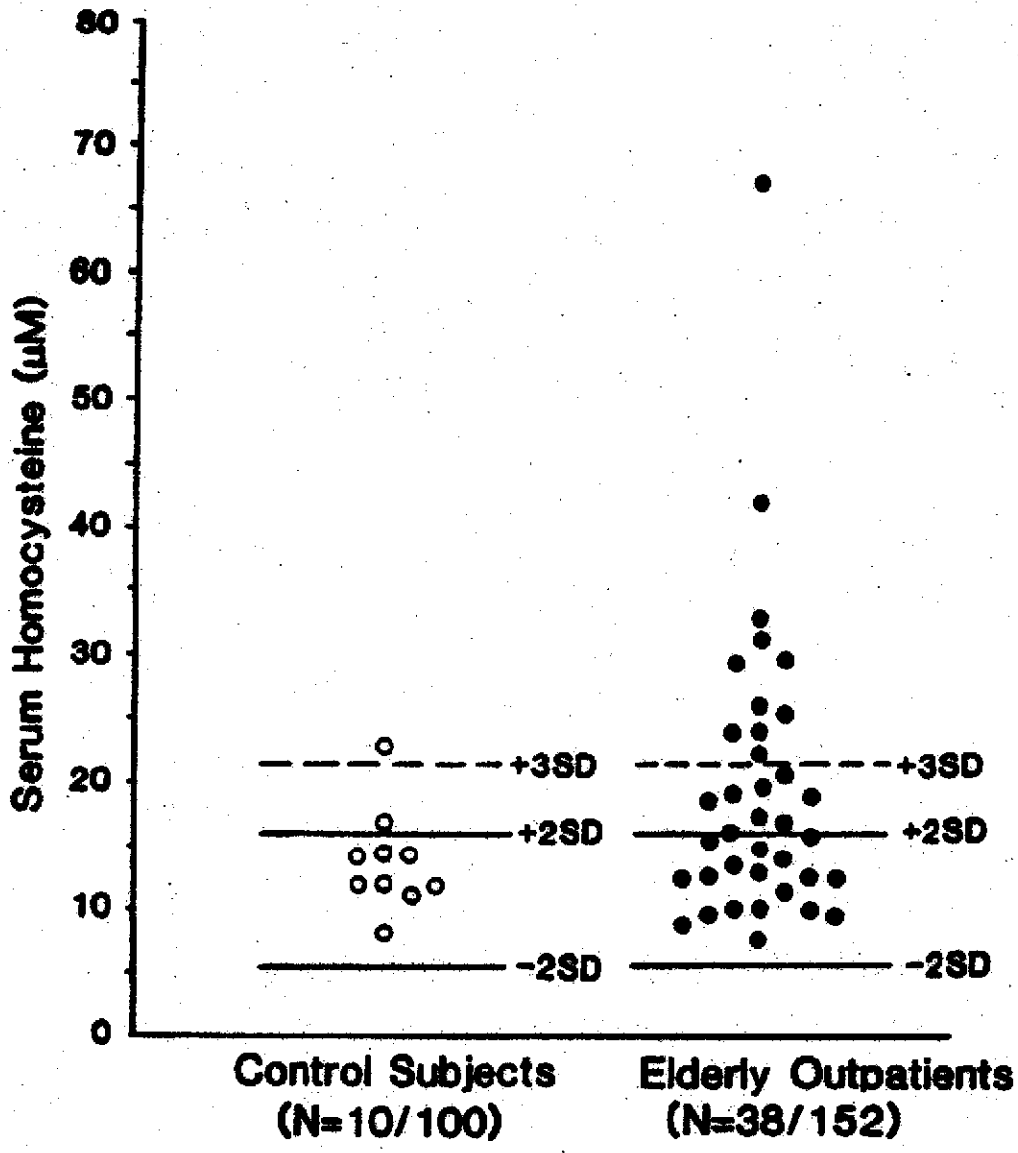
Serum Homocysteine (μM)
80
70
60
50
40
30
20
10
0
+3SD
+2SD
-2SD
+3SD
+2SD
-2SD
Control Subjects
(N=10/100)
Elderly Outpatients
(N=38/152)

FIGURE 3

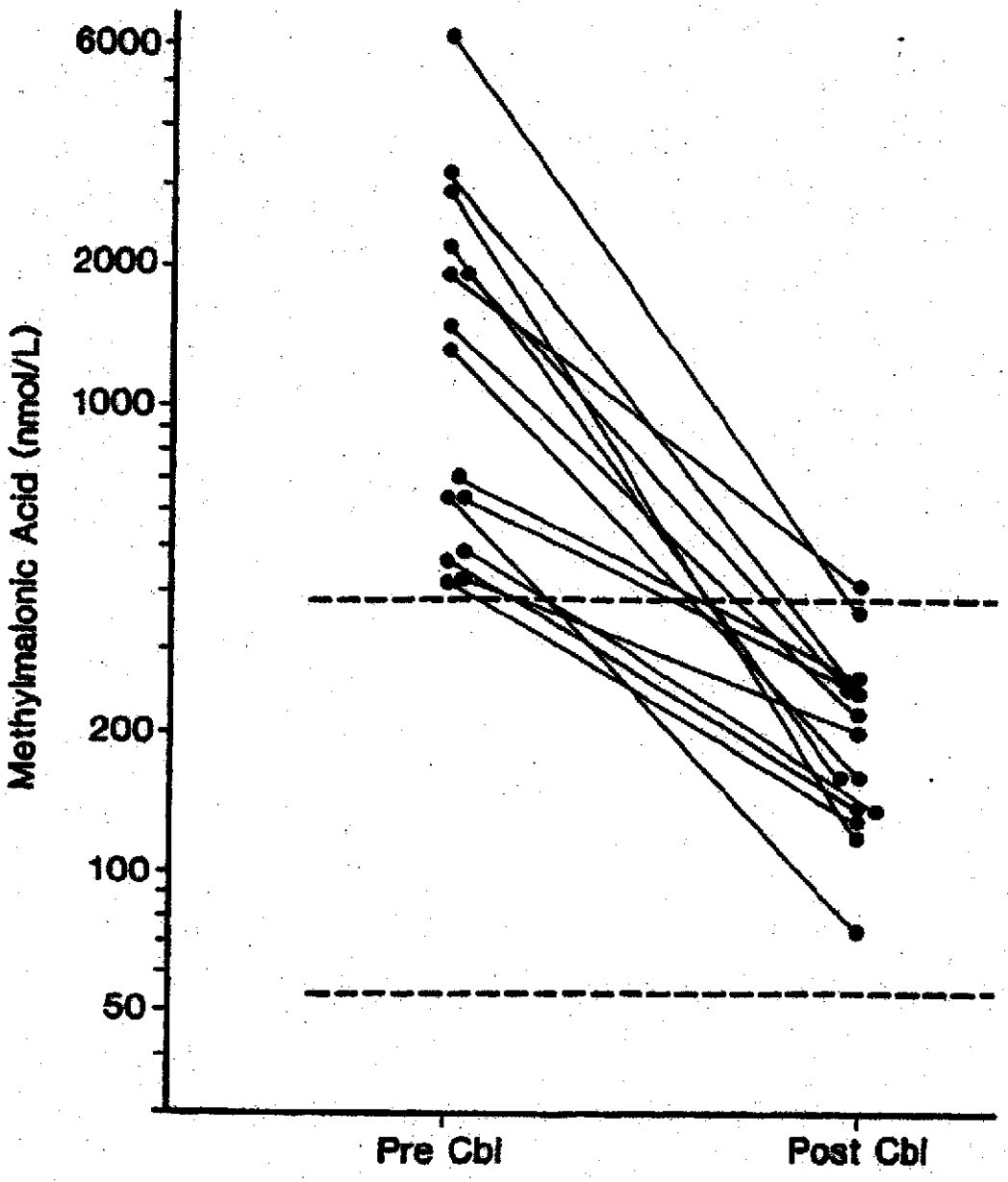
6000
2000
1000
200
100
50
Methylmalonic Acid (nmol/L)
Pre Cbl
Post Cbl

FIGURE 4

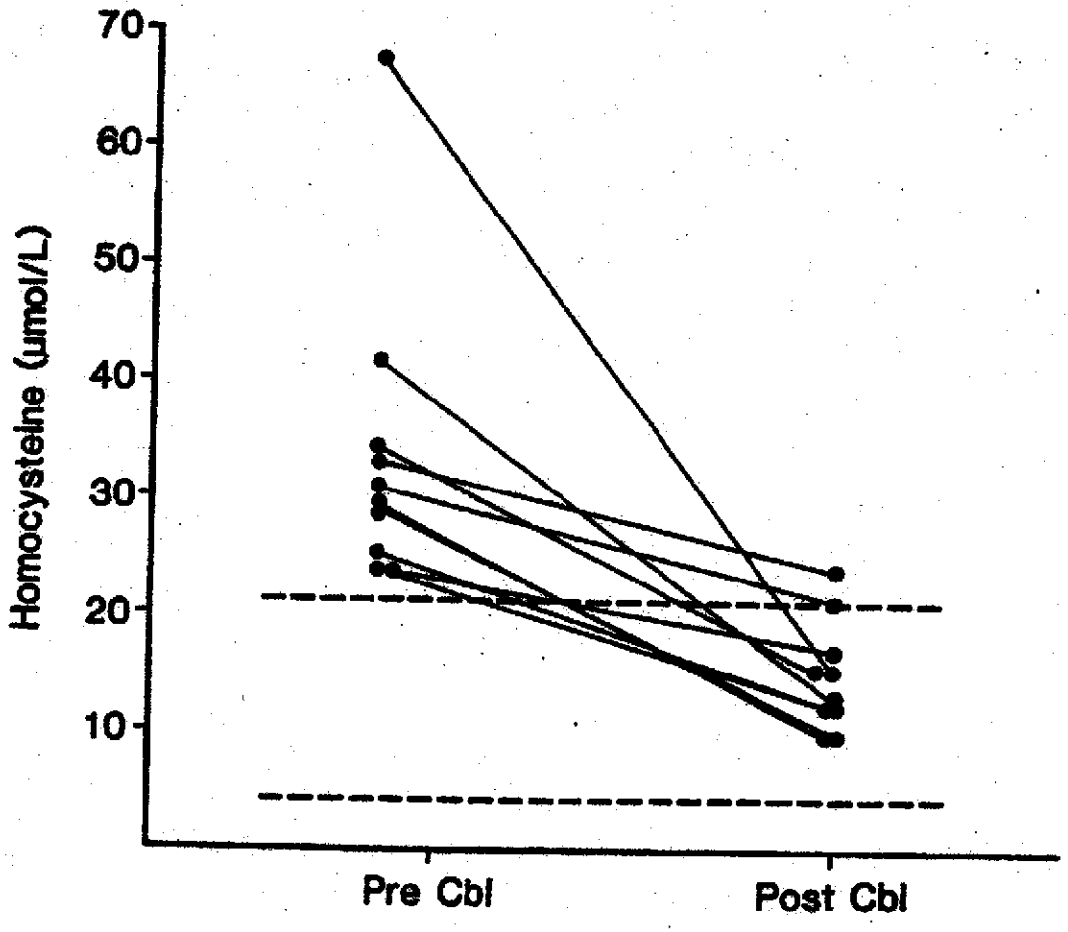

FIGURE 5

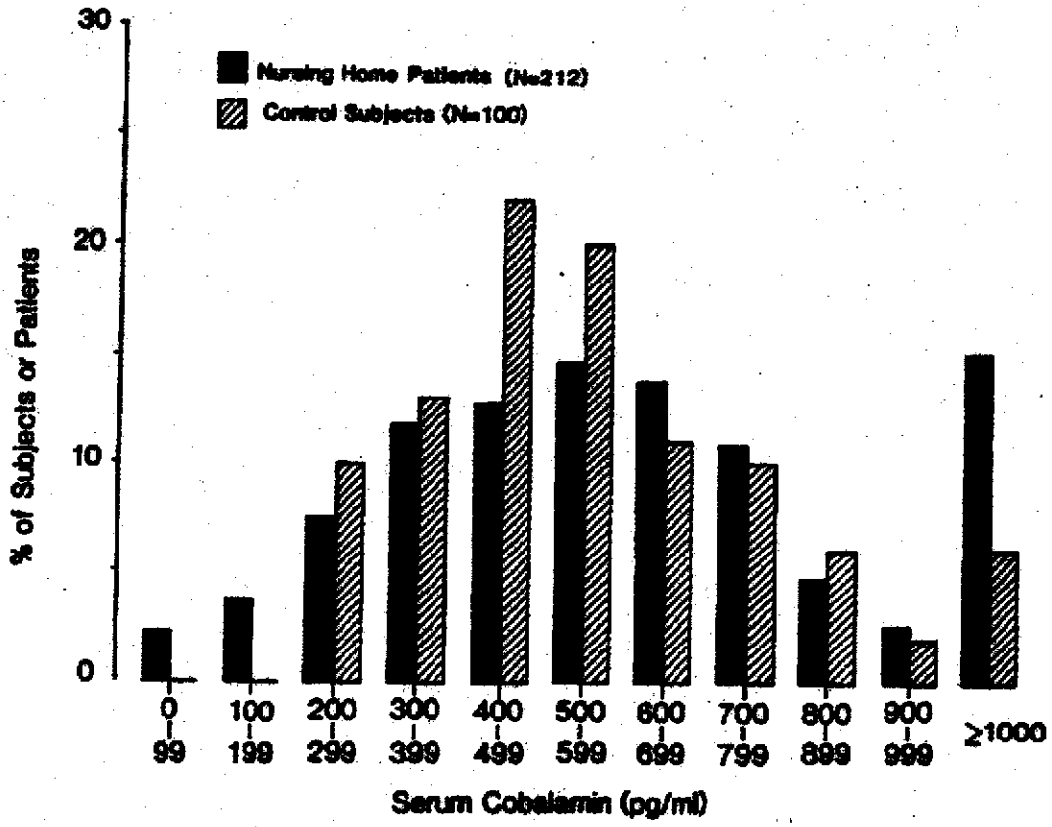
30
20
10
0
% of Subjects or Patients
Nursing Home Patients (N=212)
Control Subjects (N=100)
0 99
100 199
200 299
300 399
400 499
500 599
600 699
700 799
800 899
900 999
≥1000
Serum Cobalamin (pg/ml)

FIGURE 6

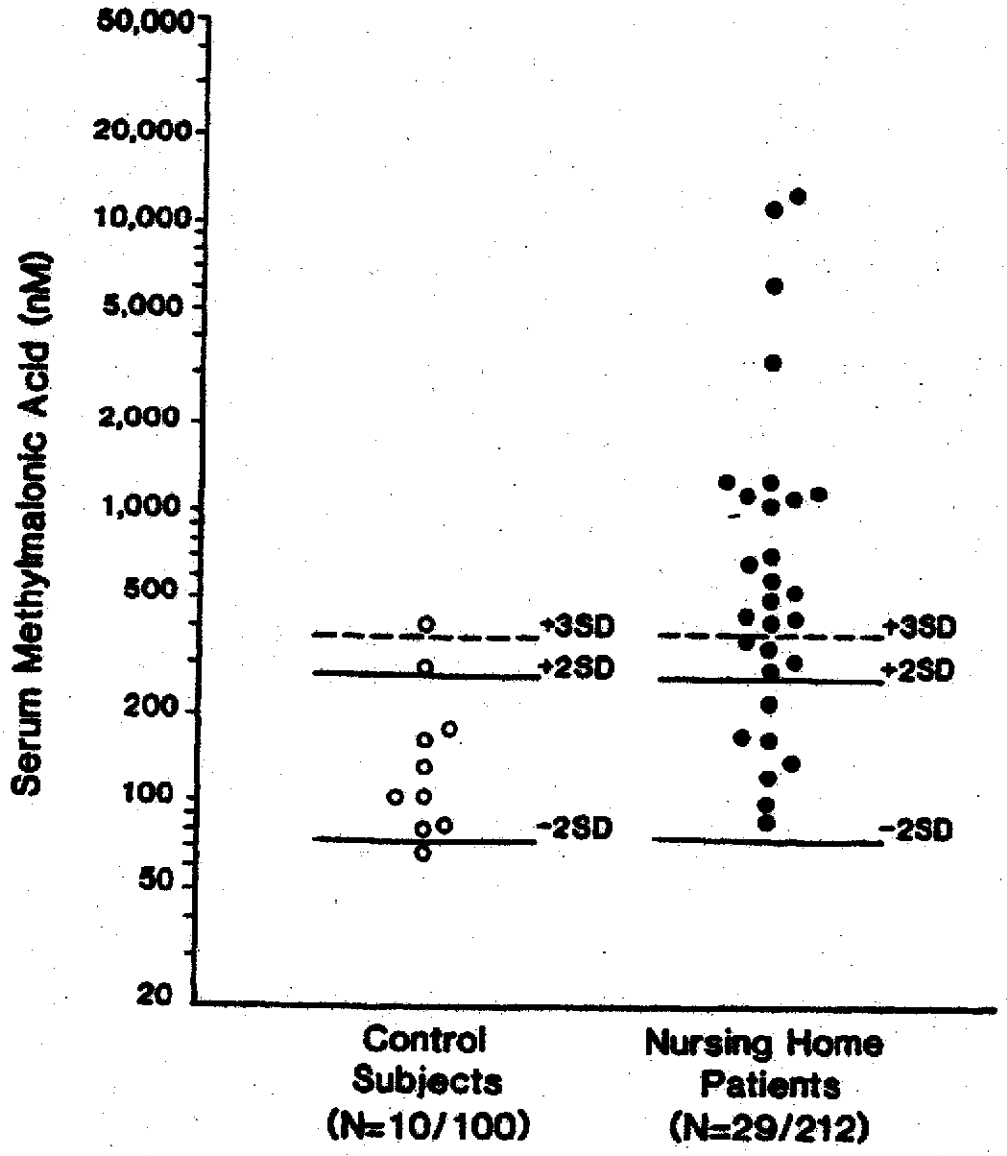
Serum Methylmalonic Acid (nM)
50,000
20,000
10,000
5,000
2,000
1,000
500
200
100
50
20
+3SD
+2SD
-2SD
+3SD
+2SD
-2SD
Control Subjects (N=10/100)
Nursing Home Patients (N=29/212)

FIGURE 7

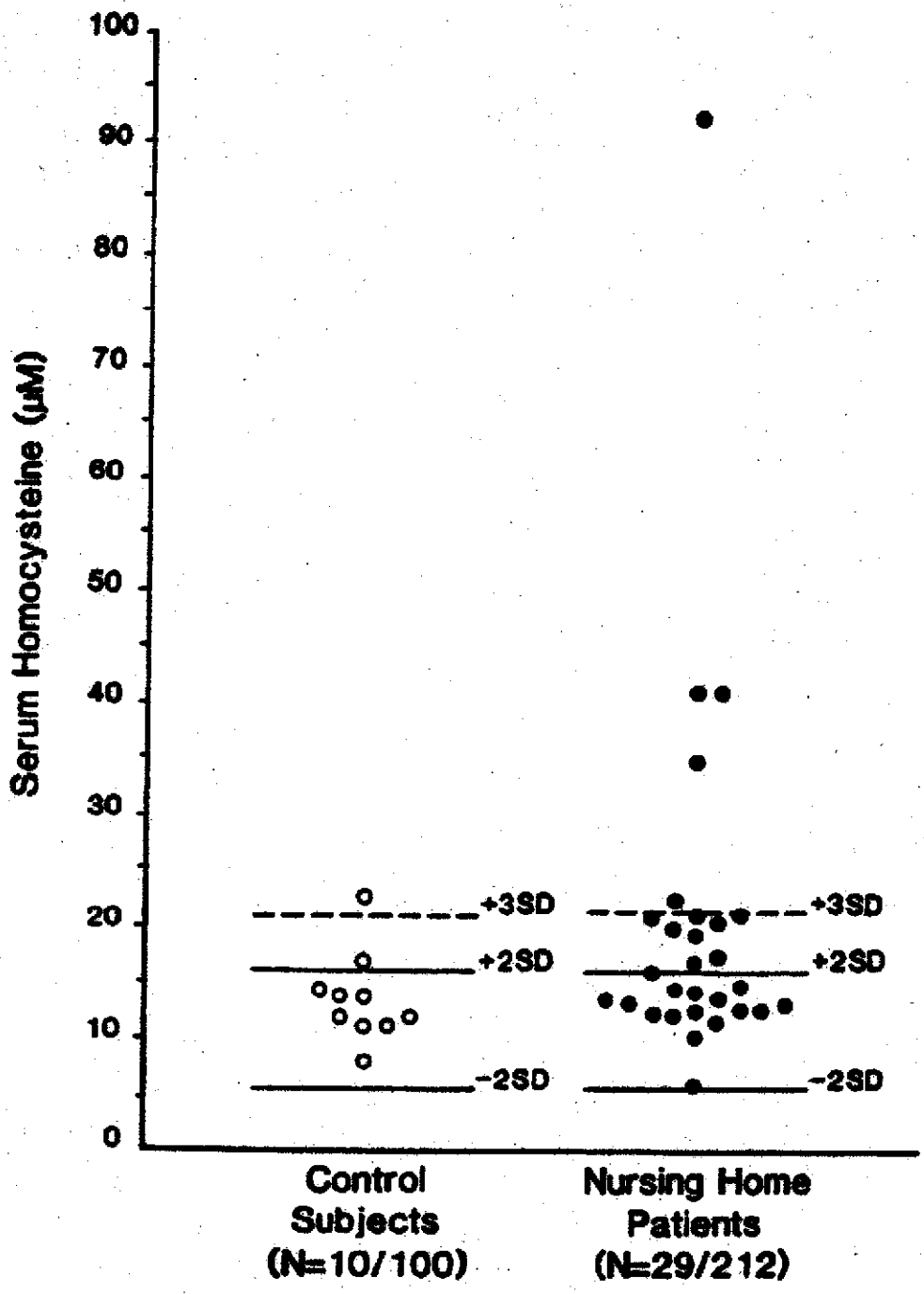
Serum Homocysteine (μM)
100
90
80
70
60
50
40
30
20
10
0
+3SD
+2SD
-2SD
+3SD
+2SD
-2SD
Control Subjects (N=10/100)
Nursing Home Patients (N=29/212)

FIGURE 8

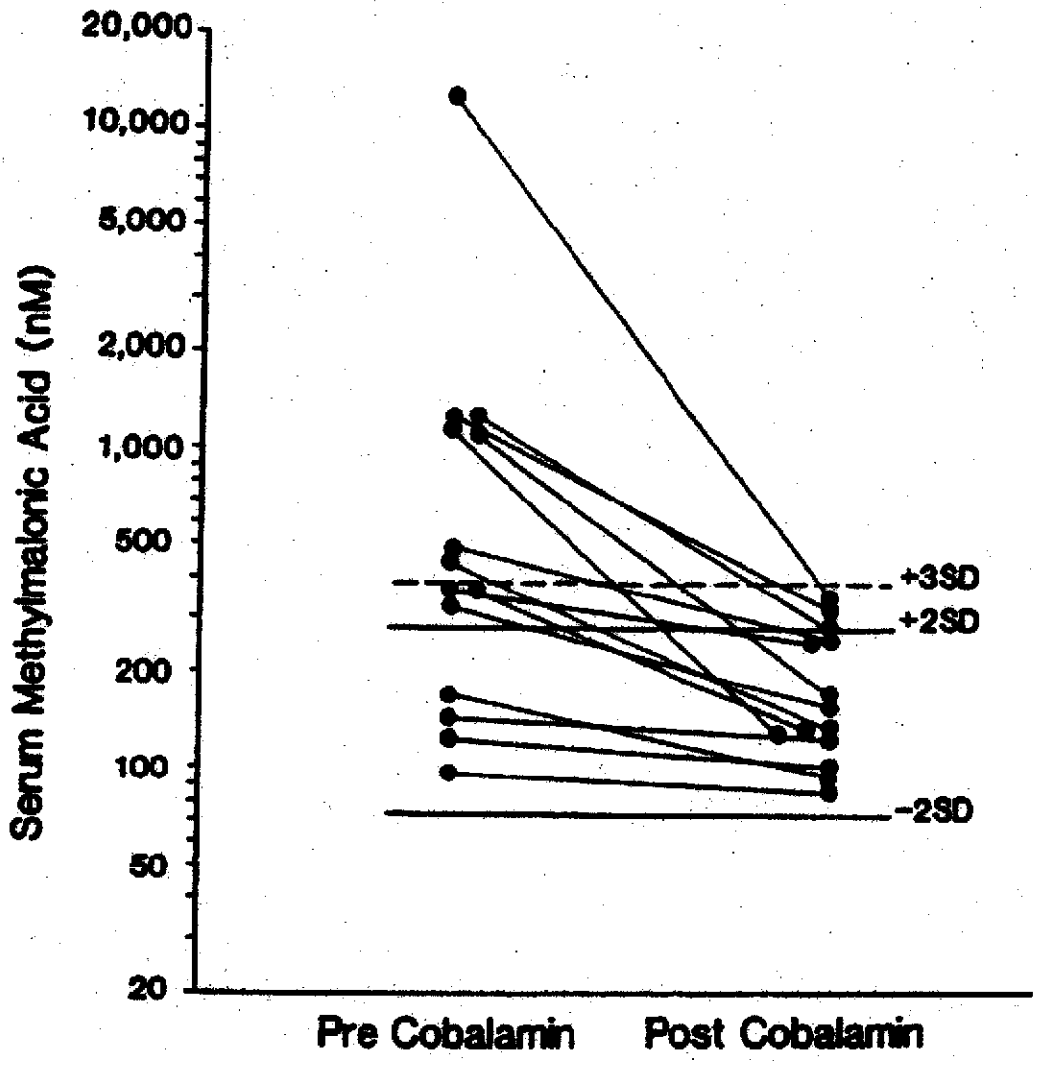
20,000
10,000
5,000
2,000
1,000
500
200
100
50
20
Serum Methylmalonic Acid (nM)
+3SD
+2SD
-2SD
Pre Cobalamin
Post Cobalamin

FIGURE 9

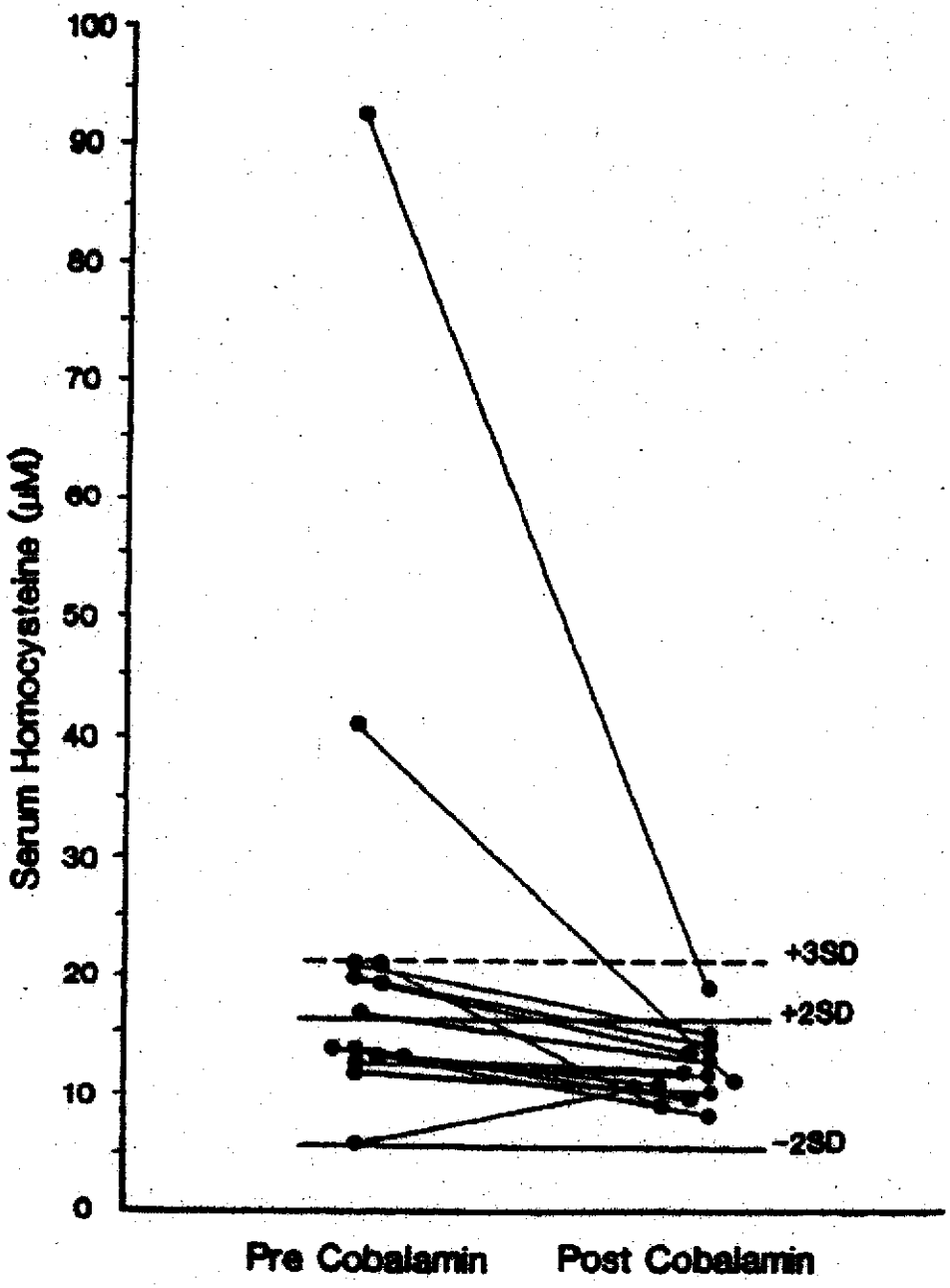
100
90
80
70
60
50
40
30
20
10
0
Serum Homocysteine (μM)
+3SD
+2SD
-2SD
Pre Cobalamin
Post Cobalamin

FIGURE 10

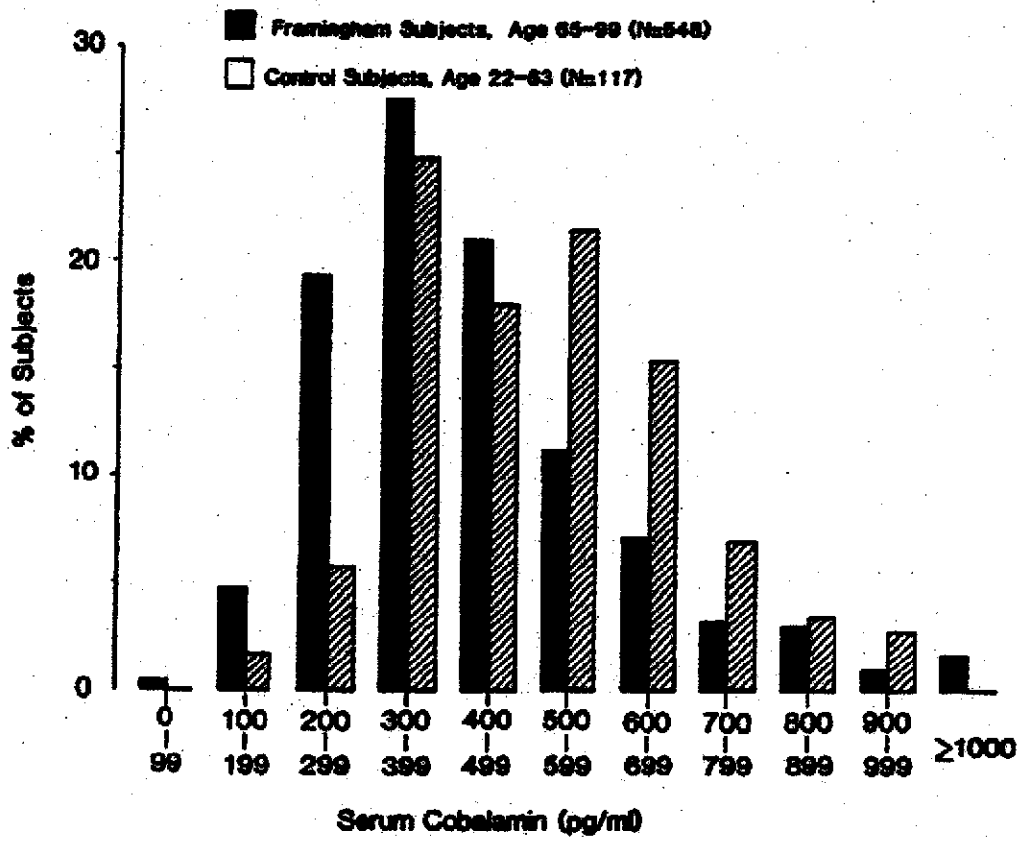
Framingham Subjects, Age 65–99 (N=548)
Control Subjects, Age 22–63 (N=117)
% of Subjects
30
20
10
0
0 99
100 199
200 299
300 399
400 499
500 599
600 699
700 799
800 899
900 999
≥1000
Serum Cobalamin (pg/ml)

FIGURE 11

COMPOSITIONS TREATING, PREVENTING OR REDUCING ELEVATED METABOLIC LEVELS

This application is a continuation of application Ser. No. 09/273,754, filed Mar. 22, 1999, now issued as U.S. Pat. No. 6,297,224, which is a continuation of application Ser. No. 09/012,955 filed Jan. 26, 1998, now issued as U.S. Pat. No. 6,207,651, which is a continuation of application Ser. No. 08/693,515, filed Aug. 2, 1996, now issued as U.S. Pat. No. 5,795,873, which is a divisional of application Ser. No. 07/999,499 filed Dec. 29, 1992, now U.S. Pat. No. 5,563,126.

FIELD OF THE INVENTION

This invention relates to the field of nutrition. Specifically, the invention is comprised of new oral vitamin preparations combining vitamin B_{12} (B_{12}, cobalamin) and folic acid (folate), and vitamin B_{12}, folate, and pyridoxine (B_6) for use in patients with elevated serum metabolite levels of homocysteine (HC), cystathionine (CT), methylmalonic acid (MMA), or 2-methylcitric acid (2-MCA). The elevation of these metabolites has been shown to be indicative of tissue deficiencies of B_{12} and/or folate and/or B_6, and related to increased risk of neuropsychiatric, vascular, renal and hematologic diseases. One embodiment of the present invention uses a non-prescription formulation comprising between 0.3–10.0 mg B_{12} and 0.1–0.4 mg folate, with the preferred embodiment using 2.0 mg B_{12} and 0.4 mg folate. Another embodiment of the non-prescription formulation uses 0.3–10 mg B_{12}, 0.1–0.4 mg folate, and 5–75 mg B_6, with the preferred embodiment using 2.0 mg B_{12}, 0.4 mg folate, and 25 mg B_6. Another embodiment of the present invention uses a prescription strength formulation comprising between 0.3–10.0 mg B_{12} and 0.4–1.0 mg folate, with the preferred embodiment using 2 mg B_{12} and 1.0 mg folate. In a further embodiment of the present invention, a prescription strength formulation is used comprising 0.3–10 mg B_{12}, 0.4–1.0 mg folate, and 5–75 mg B_6, with the preferred embodiment using 2 mg B_{12}, 1.0 mg folate, and 25 mg B_6. The formulations of the present invention eliminate the costly and time-consuming steps of distinguishing between vitamin deficiencies once a deficiency is found by measurement of serum metabolite levels. The present invention is of particular benefit to the populations at risk for tissue deficiencies of B_{12}, folate, and B_6, such as people over the age of 65, and populations that have or are at risk for neuropsychiatric, vascular, renal and hematologic diseases.

BACKGROUND

Vitamins B_{12}, folate, and B_6 are required cofactors in metabolic pathways involving methionine, homocysteine, cystathionine, and cysteine. B_{12} in the form of 5'-deoxyadenosylcobalamin is an essential cofactor in the enzymatic conversion of methylmalonylCoA to succinyl-CoA. The remethylation of homocysteine (HC) to methionine catalyzed by methionine synthase requires folate (methyltetrahydrofolate) and B_{12} in the form of methylcobalamin. HC is condensed with serine to form cystathionine (CT) in a reaction catalyzed by cystathionine □-synthase which requires B_6 (pyridoxal phosphate). CT is hydrolyzed in another B_6-dependent reaction to cysteine and □-ketobutyrate.

It is important to diagnose and treat B_{12}, folate, and B_6 deficiencies because these deficiencies can lead to life-threatening hematologic abnormalities which are completely reversible by proper treatment. B_{12} deficiency is a multisystem disorder with extremely varied clinical presentation which has been thought to occur in 0.4% of the population, e.g., about 1 million people in the United States. Symptoms of B_{12} deficiency include significant anemia, displayed for example in decreased hematocrit (e.g., <25%) or hemoglobin (e.g., ≤8 g %), with macrocytic red blood cells (i.e., mean cell volume generally greater than 100 fl), or neurologic symptoms of peripheral neuropathy and/or ataxia. See, for example, Babior and Bunn (1983) in Harrison's Principles of *Internal Medicine*, (Petersdorf et al., eds.), McGraw-Hill Book Co., New York; Lee and Gardner (1984) in Textbook of *Family Practice*, 3rd Ed. (Rakel, ed.), Saunders & Co., Philadelphia). The hematological abnormalities seen are due to intracellular folate deficiency since folate is required for a number of essential enzymatic reactions involved in DNA and RNA synthesis and since the form of folate in serum (5-methyltetrahydrofolate) must be metabolized to tetrahydrofolate by the B_{12}-dependent enzyme methionine synthase before it can be utilized by the RNA- and DNA-related enzymes. While it has been well recognized that individuals with B_{12} deficiency could display neurologic disorders in the absence of anemia, such situations were believed to be exceptional and rare. See, Beck (1985) in *Cecil Textbook of Medicine*, 17th Ed., (Wyngaarden and Smith, eds.), W. B. Saunders, Philadelphia, pp. 893–900; Babior and Bunn (1987) in *Harrison's Principles of Internal Medicine*, 11th Ed., (Braunwald et al., eds.) McGraw-Hill, New York, pp. 1498–1504; Walton (1985) in *Brain's Diseases of the Nervous System*, 9th Ed., Oxford University Press, Oxford, UK. The neurologic symptoms of B_{12} deficiency were considered to be late manifestations of the disease most typically occurring after the onset of anemia or, if they occurred first, were soon to be followed by the onset of anemia. See, Woltmann (1919) Am. J. Med. Sci. 157:400–409 Victor and Lear (1956) Am. J. Med. 20:896–911.

However, it has recently been shown that the textbook description of severe megaloblastic anemia and combined systems disease of the nervous system is the rarest presentation of B_{12} deficiency at the present time (Stabler et al. (1990) Blood 76:871–881; Carmel (1988) Arch. Int. Med. 148:1712–1714 Allen (1991) in *Cecil Textbook of Medicine*, 19th Ed., (Wyngaarden and Smith, et al. eds.), W. B. Saunders, Philadelphia, pp. 846–854.). Therefore, contrary to previous teachings, patients that may benefit from B_{12} therapy may have minimal to no hematologic changes while manifesting a wide variety of neurologic and psychiatric abnormalities (Lindenbaum et al. (1988) N. Engl. J. Med. 318:1720–1728; Greenfield and O'Flynn (1933) Lancet 2:62–63). This is particularly true for populations at risk for B_{12} deficiency, such as the elderly population (Pennypacker et al. (1992) J. Am. Geriatric Soc. 40: (in press).

The incidence of folate deficiency in the population is unknown, but has been thought to occur commonly in individuals with various degrees of alcoholism. The hematologic abnormalities seen with folate deficiency, such as macrocytic anemia, are indistinguishable from those seen with B_{12} deficiency. Folate is required for a number of essential enzymatic reactions involved in DNA and RNA synthesis, and is particularly important in rapidly dividing cells like those in the bone marrow.

B_6 is required for the first step in heme synthesis and serves a major role in transamination reactions of amino acid metabolism, in decarboxylations, and in the synthesis of the neuroactive amines histamine, tyramine, serotonin, and □-aminobutyric acid (GABA). Clinical manifestations

include microcytic hypochromic anemia, characteristic skin changes of dermatitis and acrodynia, muscular weakness, and a variety of neuropsychiatric abnormalities including hyperirritability, epileptiform convulsions, depression and confusion (Newberne and Conner (1989) in Clinical Biochemistry of Domestic Animals, Academic Press, San Diego, pp. 796–834).

Vitamin deficiencies are generally determined by measurement of serum levels. Normal serum B_{12} levels are 200–900 pg/ml, with levels of less than 100 pg/ml being said to indicate clinically significant deficiency (Beck (1985) supra) However, serum B_{12} levels are a relatively insensitive determinant of B_{12} deficiency in that only 50% of patients with clinically confirmed B_{12} deficiency have levels less than 100 pg/ml, 40% are 100–200 pg/ml, and at least 5–10% have values in the 200–300 pg/ml range. Diagnosis is further complicated by the fact that 2.5% of normal subjects (6,250,000 people in the U.S.) have low serum B_{12} levels (Allen (1991) supra), with no evidence of B_{12} deficiency and are unlikely to benefit from B_{12} therapy (Schilling et al. (1983) Clin. Chem. 29:582; Stabler (1990) supra).

Normal serum folate levels are 2.5–20 ng/ml, with levels less than 2.5 ng/ml indicating the possibility of clinically significant deficiency. Like B_{12} serum levels, however, serum folate levels are a relatively insensitive measure in that only 50–75% of patients with folate deficiency have levels less than 2.5% ng/ml, with most of the remaining 25–50% being in the 2.5–5.0 ng/ml range (Allen (1991) in *Cecil Textbook of Medicine*, 19*th Ed.*, supra)

The development of sensitive serum metabolite assays for HC, CT, MMA, and 2-MCA has allowed the relationship between metabolite levels and vitamin deficiencies to be investigated (Stabler et al. (1987) Anal. Biochem. 162:185–196; Stabler et al. (1986) J. Clin. Invest. 77:1606–1612; Stabler et al. (1988) J. Clin. Invest. 81:466–474). It has been found that elevated serum levels of HC and MMA are clinically useful tests of functional intracellular deficiencies of B_{12} and folate, with elevated HC levels seen with both B_{12} and folate deficiencies, and elevated MMA levels seen with a B_{12} deficiency (Allen et al. (1990) Am. J. Hematol. 34:9098 Lindenbaum et al. (1990) Am. J. Hematol. 34:99–107; Lindenbaum et al. (1988) N. Engl. J. Med. 318:1720–1728; Beck (1991) in Neuropsychiatric Consequences of Cobalamin Deficiency, Mosby Year Book 36:33–56 Moelby et al. (1990) 228:373–378; Ueland and Refsum (1989) J. Lab. Clin. Med. 114:473–501; Pennypacker et al. (1992) supra). Increased serum levels of CT are seen in both deficiencies and 2-MCA is elevated in B_{12} deficiency (Allen et al. (1991) in Proceedings of the 1st International Congress on Vitamins and Biofactors in Life Science, Kobe (Japan); Allen et al. (1993) Metabolism (in press)). HC and CT may be elevated in patients with intracellular deficiency of B_6, but this has not been as well documented (Park and Linkswiler (1970) J. Nutr. 100:110–116; Smolin and Benvange (1982) J. Nutr. 112:1264–1272).

Elevated serum metabolite levels are observed in disease states other than classic vitamin deficiencies. For example, elevated HC levels have been observed in the presence of vascular disease. The homocysteine theory of atherosclerosis, formulated by McCully and Wilson (1975) Atherosclerosis 22:215–227, suggests that high levels of HC are responsible for the vascular lesions seen in homocystinuria, a genetic defect caused by a deficiency in the enzyme cystathionine □-synthase. The theory also implies that moderate elevations of HC might be associated with increased risk for vascular disease (Ueland et al. (1992) in Atherosclerotic Cardiovascular Disease, Hemostasis, and Endothelial Function (Francis, Jr., ed.), Marcel Dekker, Inc., New York, pp. 183–236). Moderate hyperhomocysteinemia has been shown to be frequently present in cases of stroke and to be independent of other stroke risk factors (Brattstrom et al. (1992) Eur. J. Clin. Invest. 22:214–221). Clinical and experimental evidence demonstrates that patients who are homozygotes for cystathionine □-synthase deficiency have a markedly increased incidence of vascular disease and thrombosis. A number of studies (see, Clarke et al. (1991) N. Engl. J. Med. 324:1149–1155) strongly suggest that heterozygotes for a deficiency of cystathionine β-synthase also have an increased incidence of vascular disease and thrombosis and that such heterozygotes may constitute as many as one-third of all patients who develop strokes, heart attacks, or peripheral vascular disease under age 50. It is also likely that such heterozygotes are also at increased risk for vascular disease and thrombosis after age 50. Since the incidence of heterozygosity for cystathionine β-synthase deficiency is estimated to be 1 in 60–70, this means that there are approximately 4 million heterozygotes in the U.S. It is also possible that patients with vascular disease due to other causes, such as hypercholesterolemia, would also benefit from a decrease in their serum HC levels even if their existing levels are only slightly elevated or actually within the normal range.

Renal disease is another condition that gives rise to elevated levels of serum metabolites. Approximately 75% of patients with renal disease have elevated serum concentrations of HC, CT, MMA, and 2-MCA. Since patients with renal disease have a significant incidence and marked acceleration of vascular disease, it might be beneficial to lower their serum metabolite levels, especially that of HC.

An increasing prevalence of low serum B_{12} concentrations with advancing age has been found by many but not all investigators (Bailey et al. (1980) J. Am. Geriatr. Soc. 28:276–278 Eisborg et al. (1976) Acta Med. Scand. 200:309–314; Nilsson-Ehle et al. (1989) Dig. Dis. Sci. 34:716–723; Norman (1985) 33:374; Hitzhusen et al. (1986) Am. J. Clin. Pathol. 85:3236), folate (Magnus et al. (1982) Scan. J. Haematol. 28:360–366; Bhandell et al. (1985) J. Clin. Pathol. 38:1179–1184 Elwood et al. (1971) Br. J. Haematol. 21:557–563; Garry et al. (1984) J. Am. Geriatr. Soc. 32:71926; Hanger et al. (1991) J. Am. Geriatr. Soc. 39:1155–1159), and B_6 (Ranke et al. (1960) J. Gerontol. 15:41–44; Rose et al. (1976) Am. J. Clin. Nutr. 29:847–853; Baker et al. (1979) J. Am. Geriatr. Soc. 27:444450). Moreover, prevalence estimates for these vitamin deficiencies vary widely depending on the population groups studied. It has been unclear whether this increased prevalence is a normal age related phenomena or a true reflection of tissue vitamin deficiency and whether the low serum vitamin concentrations are a reliable indicator of functional intracellular deficiency.

It is difficult, expensive and time-consuming to distinguish between deficiencies of vitamins B_{12}, folate, and B_6. The hematologic abnormalities seen with B_{12} deficiency are indistinguishable from those seen with folate deficiency. Similarly to a B_{12} deficiency, B_6 deficiencies also result in hematologic as well as neuropsychiatric abnormalities. The traditional methods of determining deficiencies by measurement of serum vitamin levels are often insensitive. As a result, in order to determine if and which vitamin deficiency is present, a patient will be treated with one vitamin at a time and the response to that vitamin determined by normalization of serum vitamin levels and the correction of hematologic abnormalities. These steps are then repeated with each

vitamin. This method of treatment is both expensive and time-consuming. In the presence of multiple deficiencies, the diagnosis of vitamin deficiencies is further confused and give rise to the dangerous possibility that only one deficiency will be treated. For example, the hematologic abnormalities seen with a B_{12} deficiency will respond to treatment with folate alone. However, the neuropsychiatric abnormalities caused by the B_{12} deficiency will not be corrected and may indeed by worsened.

It has now been discovered for the first time that the prevalence of intracellular deficiencies of vitamins B_{12}, folate, and B_6, alone or in combination, is substantially higher than that previously estimated by measurement of serum vitamin concentrations. The present disclosure establishes that tissue deficiencies of one or more of the vitamins B_{12}, folate and B_6, as demonstrated by the elevated metabolite concentrations, occurs commonly in the elderly population even when serum vitamin levels are normal. Based on this new discovery, the present invention addresses the problem of distinguishing between vitamin deficiencies when low, low-normal, or normal serum vitamin concentrations are found by providing formulations for the treatment of high serum metabolites and at-risk populations for combinations of one or more tissue deficiencies of vitamins B_{12}, folate, and B_6.

Hathcock and Troendle (1991) JAMA 265:96–97, have suggested the treatment of pernicious anemia with an oral pill containing 300 to 1000 ug or more per day of B_{12}. However, contrary to the present invention, Hathcock and Troendle teach away from combining B_{12} therapy with folate, since "if the oral cobalamin therapy should fail to maintain adequate levels, folate might provide protection against development of anemia while permitting nerve damage from cobalamin deficiency."

U.S. Pat. No. 4,945,083, issued Jul. 31, 1990 to Jansen, entitled: Safe Oral Folic-Acid-Containing Vitamin Preparation, describes a oral vitamin preparation comprising 0.1–1.0 mg B_{12} and 0.1–1.0 mg folate for the treatment or prevention of megaloblastic anemia. This formulation presents a problem in the case of a B_{12} deficient patient, in that the 0.5 mg folate may correct the hematologic abnormalities present, but the 0.5 mg B_{12} dose may be insufficient to correct a B_{12} deficiency due to inadequate intrinsic factor. By contrast, the formulation of the present invention teaches the use of the combination of B_{12} and folate, and of B_{12}, folate and B_6, sufficient to treat either single or multiple deficiencies of B_{12}, folate, and B_6. The present invention does not rely on the determination of vitamin deficiencies by the measurement of serum vitamin levels, but uses the more sensitive measurement of elevated serum metabolites of HC, CT, MMA, and 2-MCA, shown to be related to the presence of B_{12} and/or folate and/or to B_6 deficiencies or to the presence of the increased risk of neuropsychiatric, vascular, renal, and hematologic diseases.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed.

SUMMARY OF THE INVENTION

This invention includes a method for orally administering two new vitamin preparations containing vitamin B_{12} and folate, and vitamin B_{12}, folate and B_6, for the treatment of patients with elevated serum metabolites, such as homocysteine, cystathionine, methylmalonic acid, and 2-methylcitric acid, as well as populations at risk for tissue deficiencies in one or more of the vitamins B_{12}, folate, and B_6 or for neuropsychiatric, vascular, renal, or hematologic diseases.

One embodiment of the present invention uses an over-the-counter formulation comprised of between 0.3–10 mg CN-cobalamin (B_{12}) and 0.1–0.4 mg folate. Another embodiment of the non-prescription formulation uses 0.3–10 mg B_{12}, 0.1–0.4 mg folate, and 5–75 mg B_6. Preferred embodiments of the over-the-counter formulation are comprised of about 2.0 mg B_{12} and 0.4 mg folate, and 2.0 mg B_{12}, 0.4 mg folate, and 25 mg B_6, respectively.

Another embodiment of the present invention uses a prescription formulation comprised of between 0.3–10 mg CN-cobalamin (B_{12}) and 0.4–10.0 mg folate. Another embodiment of the prescription formulation of the present invention uses 0.3–10 mg B_{12}, 0.4–10.0 mg folate, and 5–75 mg B_6. Preferred embodiments of the prescription formulation use about 2.0 mg B_{12} and 1.0 mg folate, and 2.0 mg B_{12}, 1.0 mg folate, and 25 mg B_6, respectively.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the distribution of serum B_{12} levels for a population of elderly outpatients (ages 65–99, n=152) and a normal population (ages 17–65, n=100).

FIG. 2 shows serum MMA levels for a population of elderly outpatients with serum B_{12} values<300 pg/ml (ages 65–99, n=38/152) and a normal population with serum B_{12} values<300 pg/ml (ages 17–65, n=10/100)

FIG. 3 shows serum HC levels for a population of elderly outpatients with serum B_{12} values<300 pg/ml (ages 65–99, n=38/152) and a normal population with serum B_{12} values<300 pg/ml (ages 17–65, n=10/100).

FIG. 4 shows serum MMA levels before and after treatment with parenteral cobalamin for a population of elderly outpatients with elevated MMA values and serum B_{12} values<300 pg/ml (ages 65–99, n=15/38).

FIG. 5 shows serum HC levels before and after treatment with parenteral cobalamin for a population of elderly outpatients with elevated HC values and serum B_{12} values of<300 pg/ml (ages 65–99, n=10/38)

FIG. 6 shows the distribution of serum B_{12} levels for a population of elderly nursing home patients (ages 55–107, n=212) and a normal population (ages 17–65, n=100).

FIG. 7 shows serum MMA levels for a population of elderly nursing home patients with. serum B_{12} values<300 pg/ml (ages 55–107, n=29/212) and a normal population with serum B_{12} values (ages 17–65, n=10/100).

FIG. 8 shows serum HC levels for a population of elderly nursing home patients with serum B_{12} values<300 pg/ml (ages 55–107, n=29/212) and a normal population with serum B_{12} values<300 pg/ml (ages 17–65, n=10/100).

FIG. 9 shows serum MMA levels before and after treatment with parenteral cobalamin for a population of elderly nursing home patients with serum B_{12} values<300 pg/ml (ages 55–107, n=14/29).

FIG. 10 shows serum HC levels before and after treatment with parenteral cobalamin for a population of elderly nursing home patients with serum B_{12} values<300 pg/ml (ages 55–107, n=14/29).

FIG. 11 shows the distribution of serum B_{12} levels for a population of elderly patients (ages 65–99, n=548) and a normal population (ages 22–63, n=117) (Framingham study).

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to the presently preferred embodiments of the invention, which, together

with the following examples, serve to explain the principles of the invention.

This invention uses new oral vitamin formulations combining vitamin B_{12} (B_{12}, cobalamin) and folic acid (folate), and vitamin B_{12}, folate and pyridoxine (B_6). The formulations of the present invention are for use in the treatment of elevated serum levels of one or more of the metabolites homocysteine (HC), cystathionine (CT), methylmalonic acid (MMA), or 2-methylcitric acid (2-MCA). The use of the formulations of the present invention further include as a method of lowering serum metabolite levels of one or more of HC, CT, MMA, or 2-MCA, where these metabolite levels are not elevated but the patients are at risk for or have neuropsychiatric, vascular, renal, or hematologic diseases.

One embodiment of the present invention uses a non-prescription formulation comprised of between about 0.3–10 mg CN-cobalamin (B_{12}) and 0.1–0.4 mg folate. Another embodiment of the present invention uses a non-prescription formulation comprised of between about 0.3–10 mg B_{12}, 0.1–0.4 mg folate, and 5–75 mg B_6. Preferred embodiments of the non-prescription formulation are comprised of about 2.0 mg B_{12} and 0.4 mg folate, and 2.0 mg B_{12}, 0.4 mg folate, and 25 mg B_6, respectively.

Another embodiment of the present invention is comprised of a prescription formulation comprised of between about 0.3–10 mg B_{12} and 0.4–10.0 mg folate, with the preferred embodiment comprised of about 2.0 mg B_{12} and 1.0 mg folate. Another embodiment of the prescription strength formulation is comprised of about 0.3–10 mg B_{12}, 0.4–10.0 mg folate, and 5–75 mg B_6, with a preferred embodiment comprised of about 2.0 mg B_{12}, 1.0 mg folate, and 25 mg B_6.

The formulations of the present invention are for the treatment and prevention of elevated metabolite levels in at risk populations, such as the elderly, and people that have or are at risk for neuropsychiatric, vascular, renal and hematologic diseases. The present invention eliminates the costly and time consuming need to differentiate between B_{12}, folate, and B_6 deficiencies.

The administration of a daily dose of the vitamin formulations of the present invention provides better long-term normalization of serum HC and other metabolites than prior art formulations, and eliminates the difficulty in differentiating between deficiencies of two or three of the vitamins, the difficulty in diagnosing multiple deficiencies of two or three of the vitamins, and the expense of doing so. Further, the administration of an oral preparation of B_{12} and folate, with or without B_6, is preferred over intramuscular injections for patient convenience and ease of administration.

For example, the inclusion of B_{12} will be useful as a safeguard for patients misdiagnosed folate deficient, even though they are actually B_{12} deficient, since treatment with folate alone in such patients is extremely dangerous. The danger arises from the fact that treating a B_{12} deficient patient with folate alone may reverse or prevent the hematologic abnormalities seen in B_{12} deficiency, but will not correct the neuropsychiatric abnormalities of a B_{12} deficiency and may actually precipitate them. Even in the absence of intrinsic factor, approximately 1% of a 2.0 mg oral dose of B_{12} is absorbed by diffusion. Thus, approximately 20 ug of B_{12} would be absorbed from the formulations of the present invention which would be more than adequate even in patients with pernicious anemia who have lost their intrinsic factor-facilitated absorption mechanism for B_{12}. The inclusion of folate will be of benefit since B_{12} deficiency causes a secondary intracellular deficiency of folate. The inclusion of folate and B_6 will also be of benefit in patients with mixed vitamin deficiencies.

The formulations of the present invention may be administered as a non-injectable implant or orally. Non-injectable use may be as a patch. Formulations for oral administration are preferably encapsulated. Preferably, the capsule is designed so that the formulation is released gastrically where bioavailability is maximized. Additional excipients may be included to facilitate absorption of the vitamin formulations. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders may also be employed.

Example 1 describes the methods used to measure serum vitamin and metabolite levels. Example 2 describes a new study conducted with 412 subjects over the age of 65 with a variety of medical conditions correlating the incidence of low serum vitamin levels with elevated serum metabolite levels. A study determining the incidence of undetected B_{12} deficiency and response of serum MMA and HC to B_{12} treatment in a geriatric outpatient population is described in Example 3. Example 4 describes a similar study conducted with a geriatric nursing home population, and Example 5 describes a similar study conducted with another geriatric population.

EXAMPLE 1

Methods for Measurement of Serum Vitamin and Metabolite Levels

Serum vitamin assays. Serum vitamins B_{12} and folate were measured by a quantitative radioassay method using purified intrinsic factor and purified folate binding protein. Vitamin B_6 was measured by a radioenzymatic assay method wherein serum is incubated with apoenzyme tosine-decarboxylase, C_{14} labelled tyrosine is added to start the enzymatic reaction which is stopped with HCl. Subsequently the free C_{14}-labelled CO_2 is adsorbed by a KOH impregnated filtering paper. The measured C_{14} activity is directly proportional to the B_6 (pyridoxal phosphate) concentration (Laboratory Bioscientia, Germany).

Serum metabolite assays. Serum metabolite assays for homocysteine and methylmalonic acid were conducted by the capillary gas chromatography and mass spectrometry methods of Marcell et al. (1985) Anal. Biochem. 150:58; Stabler et al. (1987) supra, and Allen et al. (1990) Am. J. Hematol. 34:90–98. Serum cystathionine levels were assayed by the method of Stabler et al. (1992) Blood (submitted). Serum 2-methylcitric acid was assayed by the method of Allen et al. (1993) Metabolism supra.

Statistical methods. Statistical analysis was done with the SAS statistical package (version 6.06). Nonparametric data for two or more groups were tested with the two sample Wilcoxon rank sum test (with Bonferroni's correction for the significance level α) and the Kruskall Wallis test. From the results of the healthy young subjects reference intervals were calculated. Since the frequency distribution of the values of each parameter were markedly abnormal they were transformed to normal distributions using log transformation. The sample prevalence p with 95% confidence intervals of low serum vitamins B_{12}, folate, and B_6 concentrations was calculated as $(p \pm 2\sqrt{p(1-p)/n}) \times 100$ wherein n is the total sample size, p is the number of low serum vitamin concentrations/n; low serum concentrations are defined as <mean −2 S.D.

EXAMPLE 2

Incidence of Elevated MMA, 2-MCA, HC, and CT Levels in the Geriatric Population

The serum concentrations of B_{12}, folate, and B_6 were measured in 412 subjects over the age of 65 (subgroups

A–D), and in 99 healthy control subjects aged 20–55 years (subgroup E). The geriatric subgroups were defined as follows: A, 110 patients with atherosclerosis; B, 98 patients with neuropsychiatric disorders; C, 102 patients with atherosclerosis and multiple diseases including rheumatoid arthritis and diabetes; D, 102 subjects who were healthy.

Venous blood was obtained from all subjects in the morning after an overnight fast. The blood was spun within one hour after collection and the serum was transported in dry ice to the central laboratory. Serum vitamins B_{12} and folate were measured as described in Example 1 with a vitamin B_{12}/folate dual RIA kit (CT301/CT302 Amersham Buchler, UK). Vitamin B_6 and serum metabolites were measured as described in Example 1.

Since renal function can influence serum metabolite concentrations (Ueland and Refsum (1989) supra Moelby et al. (1992) Scand. J. Clin. Lab. Invest. 52:351–354), serum creatinine concentrations were measured in all subjects by the Jaffe photometric method (Laboratory Bioscientia, Germany). Normal range was 62–124 μmol/L. Creatinine clearance was calculated using the formulation of Cockroft and Gault (1976) Nephron 16:31–41.

Normal ranges for serum vitamin and metabolite levels were determined by the mean±2 standard deviations after log normalization using the values from subgroup E. Results are shown in Table 1:

TABLE 1

INCIDENCE OF LOW SERUM VITAMIN AND HIGH METABOLITE LEVELS IN GERIATRIC POPULATIONS A–D AND A YOUNGER HEALTHY POPULATION E.

Group	B_{12}	Folic Acid	B_6	MMA	2-MCA	HC	CT
A	6%	12%	48%	36%	44%	55%	64%
B	6%	19%	53%	47%	39%	59%	6%
C	3%	10%	50%	32%	45%	39%	73%
D	6%	6%	17%	26%	23%	38%	41%
E	2%	1%	1%	3%	6%	2%	4%

There was a rough correlation with low vitamin levels and elevated metabolites, but many of the patients with elevated metabolites had low normal or normal vitamin levels. Correlations between clinical abnormalities within groups A, B, and C were not present. Patients were treated with weekly injections of a multi-vitamin preparation containing 1.0 mg B_{12}, 1.1 mg folate, and 5 mg B_6, resulting in a marked lowering or normalization of elevated metabolite levels in virtually every elderly patient.

These data support the conclusions that there is an increased incidence of low levels of serum B_{12}, folate, and B_6 in the geriatric population, and that serum MMA, 2-MCA, HC and CT are elevated in an even higher percentage of geriatric patients. The presence of elevated levels of one or more of the metabolites HC, CT, MMA, or 2-MCA indicate a tissue or intracellular deficiency of one or more of the vitamins B_{12}, folate and B_6. It not possible to tell without expensive, time-consuming, and extensive testing which one vitamin or pair of vitamins, or whether all three vitamins are deficient. These observations, together with the fact that elevated metabolite levels are corrected by parenteral therapy with a combination of vitamins B_{12}, folate, and B_6, indicate that a tissue deficiency of one or more of these vitamins occurs commonly in the geriatric population and that measurement of serum vitamin levels alone is an inadequate method for identifying such deficiencies.

EXAMPLE 3

Determination of Serum B_{12} Folate, MMA, HC, CT and 2-MCA Levels in a Geriatric Outpatient Population

A study was conducted with 152 elderly outpatient subjects to measure the prevalence of B_{12} deficiency in geriatric outpatients as determined by both low serum B_{12} levels and elevations of MMA and HC, and to determine the response to B_{12} treatment. Blood samples were obtained on 152 consecutive geriatric outpatients, ages 65–99. Control values were determined from 100 subjects, ages 17–65. Serum B_{12} folate, MMA HC, CT, and 2-MCA levels were obtained for each patient, shown in Table 2. The significance of the results marked as "***" in Table 2 are as follows: B_{12} levels of<200 pg/ml; folate<3.8 ng/ml; homocysteine>16.2 uM; MMA>271 nM; CT>342 nM; and 2-MCA>228 nM. Serum MMA, HC, CT, and 2-MCA levels were measured as described in Example 1. Serum B_{12} and folate were measured as described in Example 1 using a Corning Immophase kit (CIBA-Corning, Medfield, Mass.) with the normal range defined as 200–800 pg/ml for B_{12} and 3.8 ng/ml for folate. After evaluation, patients received weekly parenteral cyanocobalamin injections (1,000 ug IM) for 8 weeks, followed by monthly injections. Repeat laboratory and clinical assessments were administered at 8 weeks and at 6 months.

Results show that 25% of the subjects had a serum B_{12} level≦300 pg/ml and 8.5% had a low level of<200 pg/ml. FIG. 1 shows the shift seen in elderly subject towards lower serum B_{12} levels. More than half of the subjects with low or low-normal serum B_{12} levels had elevations of MMA (FIG. 2) and/or HC (FIG. 3) greater than 3 S.D. above the means in normals and representing 14.5% of the total screened population.

Patients with low and low/normal serum B_{12} levels were treated with weekly injections of 1.0 mg B_{12}. Parenteral B_{12} administration caused elevated metabolite levels to fall to or towards normal (FIGS. 4 and 5) in every subject treated with B_{12}. It appears that the true prevalence of previously unrecognized B_{12} deficiency in this elderly population was at least 14.5%.

It can be seen from the data presented in Table 2 that serum B_{12} levels are insensitive for screening B_{12} deficiencies since similar numbers of patients with low normal serum B_{12} levels of 201–300 pg/ml compared with patients with low B_{12} levels (≦200 pg/ml) had markedly elevated metabolites which fell with B_{12} treatment. Further, this study shows that elderly patients have a high incidence (at least 14.5%) of unrecognized B_{12} deficiency, detectable by measurement of serum HC and MMA levels in patients with serum B_{12} levels<300 pg/ml.

A further finding in this study emphasizes the need to treat elevated metabolite levels with a combination of vitamin B_{12} and folate with or without B_6. Some of the patients exhibiting elevated metabolite levels did not fully respond to B_{12} treatment. This may indicate a concomitant deficiency of folate and/or B_6. The lack of response to B_{12} treatment could result from a deficiency of one, a pair, or all three vitamins. However, it would be expensive and time-consuming to attempt to distinguish between the vitamin deficiencies.

Another, and perhaps the most important, finding in this study is the large number of patients with serum B_{12}>300 pg/ml who have elevated values for one or more metabolites as indicated by a "***" next to the individual values. As can readily be seen in Table 2, there are many examples of elevated value for MMA and/or 2-MCA at all levels of serum B_{12} including the mid-normal (300–600 pg/ml), the high-normal (600–800 pg/ml), and even the elevated (>800 pg/ml) ranges. The same is true for elevations of HC and CT. In some patients the serum folate is low, indicating that folate deficiency may be present, but in many cases both B_{12}

and folate levels are normal. B_6 levels were not performed in this study, but B_6 deficiency would not be expected to cause elevations of MMA or 2-MCA. Thus in many patients it is not clear which vitamin, or pair of vitamins, or whether all three vitamins is or are deficient. One could pick a single vitamin, often at random, with which to treat a patient for several weeks or months, and then repeat measurement of metabolite levels to determine if a partial or full correction had occurred. If there was no response, one could try another vitamin, or if there was a partial response one could add a second vitamin, and then repeat metabolite measurement after several weeks or months. If there was still no response, one could try the third vitamin, or if there was a partial response, one could try a different pair of vitamins. Eventually one could determine whether an individual vitamin, a particular pair of vitamins, or all three vitamins were required to normalize or maximally reduce the metabolite levels, but it would often require months or even a year to make this determination. Such a determination would be expensive. In addition, a patient who was optimally treated with a single vitamin or pair of vitamins might subsequently develop a deficiency of one or even two of the other vitamins as evidenced by a re-elevation or increase in the levels of one or more metabolites. Therapeutic testing could be reinitiated and continued as described above, although this would also be time-consuming and expensive.

It requires less time and expense to treat patients with elevated metabolite levels with a combination of vitamin B_{12} and folate, or a combination of vitamin B_{12}, folate and vitamin B_6. The utility of the approach of the present invention is appreciated only after it is taught, for the first time in the present disclosure, that a deficiency of one or more of the three vitamins occurs commonly in the elderly population as evidenced by elevation of one or more metabolites, i.e., MMA, 2-MCA, HC and CT.

EXAMPLE 4

Determination of Serum B_{12}, Folate, MMA, and HC Levels in a Geriatric Nursing Home Population

A study was conducted with 212 elderly nursing home patients to determine serum B_{12}, folate, MMA, and HC levels (Table 3). The significance of the results shown in Table 3 marked with "**" are as described for Table 2 (Example 3). The control group consisted of 100 subjects between the ages of 17–65 years. As in the study described in Example 3, the elderly population exhibited a shift to lower serum B_{12} levels (FIG. 6), elevated serum MMA (FIG. 7) and HC (FIG. 8) levels. Parenteral administration of B_{12} 1 mg per week for 8 weeks to those with serum B_{12}<300 pg/ml caused elevated MMA (FIG. 9) and HC (FIG. 10) levels to fall to or towards normal.

As in the study reported in Example 3, a further finding in this study emphasizes the need to treat elevated metabolite levels with a combination of vitamins B_{12} and folate, with or without B_6. Some of the patients exhibiting elevated metabolite levels did not fully respond to B_{12} treatment. This may indicate a concomitant deficiency of folate and/or B_6. The lack of response to B_{12} treatment could result from a deficiency of one, a pair, or all three vitamins. However, it would be expensive and time-consuming to attempt to distinguish between the vitamin deficiencies.

Again, an important finding in this study is the large number of patients with serum B_{12}>300 pg/ml who have elevated values for one or more metabolites as indicated by a "**" next to the individual values. As is seen in Table 3, there are many examples of elevated values for MMA at all levels of serum B_{12} including the mid-normal (300–600 pg/ml), the high-normal (600–800 pg/ml), and even the elevated (>800 pg/ml) ranges. The same is true for elevations of HC. In some patients the serum folate is low, indicating that folate deficiency may be present, but in many cases both B_{12} and folate levels are normal. B_6 levels were not performed in this study, but B_6 deficiency would not be expected to cause elevations of MMA. Thus, again it is not clear which vitamin, or pair of vitamins, or whether all three vitamins is or are deficient. One could pick a single vitamin with which to treat a patient for several weeks or months, and then repeat measurement of metabolite levels to determine if a partial or full correction had occurred. If there was no response, one could try another vitamin, or if there was a partial response one could add a second vitamin, and then repeat metabolite measurement after several weeks or months. If there was still no response, one could try the third vitamin, or if there was a partial response, one could try a different pair of vitamins. Eventually one could determine whether an individual vitamin, a particular pair of vitamins, or all three vitamins were required to normalize or maximally reduce the metabolite levels, but it would often require months or even a year to make this determination. Such a determination would be expensive. In addition, a patient who was optimally treated with a single vitamin or pair of vitamins might subsequently develop a deficiency of one or even two of the other vitamins as evidenced by a re-elevation or increase in the levels of one or more metabolites. Therapeutic testing could be reinitiated and continued as described above, although this would also be time-consuming and expensive.

It requires less time and expense to treat patients with elevated metabolite levels with a combination of vitamin B_{12} and folate, or a combination of vitamin B_{12}, folate and vitamin B_6. The utility of the approach of the present invention is appreciated only after it is taught, for the first time in the present disclosure, that a deficiency of one or more of the three vitamins occurs commonly in the elderly population as evidenced by elevation of one or more metabolites, i.e., MMA, 2-MCA, HC and CT.

EXAMPLE 5

Determination of Serum B_{12} Folate, MMA, and HC Levels in a Geriatric Population

A study was conducted with 548 elderly subjects from the Framingham study between the ages of 65–99 to determine serum B_{12}, folate, MMA, and HC levels (Table 4). The significance of the results shown in Table 4 (marked with "**") are as described for Table 2 (Example 2).

As in the study described in Examples 3 and 4, the elderly population exhibited a shift to lower serum B_{12} levels (FIG. 11), and elevated serum MMA and HC levels. The elderly population also exhibited a high incidence (9.5%) of low serum folate levels (Table 4). As in the studies reported in Examples 2, 3 and 4, the incidence of tissue or intracellular vitamin deficiencies based on elevated metabolite levels was higher than that predicted from measurement of serum vitamin levels.

As in Examples 3 and 4 above, these results confirm the importance of the finding that there are a large number of patients with serum B_{12}>300 pg/ml who have elevated values for one or more metabolites as indicated by a "**" next to the individual values. As is seen in Table 4, there are many examples of elevated MMA values at all levels of

serum B_{12} including the mid-normal (300-600 pg/ml), the high-normal (600–800 pg/ml), and even the elevated (>800 pg/ml) ranges. The same is true for elevations of HC. In some patients the serum folate is low, indicating that folate deficiency may be present, but in many cases both B_{12} and folate levels are normal. B_6 levels were not performed in this study, but B_6 deficiency would not be expected to cause elevations of MMA. Thus, again it is not clear which vitamin, or pair of vitamins, or whether all three vitamins is or are deficient. One could pick a single vitamin with which to treat a patient for several weeks or months, and then repeat measurement of metabolite levels to determine if a partial or full correction had occurred. If there was no response, one could try another vitamin, or if there was a partial response one could add a second vitamin, and then repeat metabolite measurement after several weeks or months. If there was still no response, one could try the third vitamin, or if there was a partial response, one could try a different pair of vitamins. Eventually one could determine whether an individual vitamin, a particular pair of vitamins, or all three vitamins were required to normalize or maximally reduce the metabolite levels, but it would often require months or even a year to make this determination. Such a determination would be expensive. In addition, a patient who was optimally treated with a single vitamin or pair of vitamins might subsequently develop a deficiency of one or even two of the other vitamins as evidenced by a re-elevation or increase in the levels of one or more metabolites. Therapeutic testing could be reinitiated and continued as described above, although this would also be time-consuming and expensive.

It requires less time and expense to treat patients with elevated metabolite levels with a combination of vitamin B_{12} and folate, or a combination of vitamin B_{12}, folate and vitamin B_6. The utility of the approach of the present invention is appreciated only after it is taught, for the first time in the present disclosure, that a deficiency of one or more of the three vitamins occurs commonly in the elderly population as evidenced by elevation of one or more metabolites, i.e., MMA, 2-MCA, HC and CT.

TABLE 2

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC OUTPATIENT POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA	CT	Total MC
116	66**	9.8	41.8**	1508**	507**	759**
118	79**	9.3	29.6**	2200**	343**	428**
016	155**	7.6	15.3	1316**	208	196
067	163**	6.6	9.9	93	164	69
091	178**	12.0	29.2**	3108**	438**	318**
042	181**	11.3	13.0	452**	300	262**
030	185**	6.6	26.0**	282**	310	223
037	187**	9.4	12.3	160	218	334**
100	187**	9.5	13.6	208	453**	141
036	188*	9.9	16.3**	298**	385**	322**
109	189**	7.6	12.3	127	188	161
007	191**	11.7	67.1**	6349**	619**	1005**
018	193**	5.8	16.7**	412	272	235**
050	210	4.0	25.3**	464**	727**	121
108	214	6.0	31.1**	264	523**	315**
041	216	7.2	19.1**	418**	360**	288*
126	224	6.5	8.8	103	361**	121
005	231	12.5	17.1**	269	825**	276**
024	235	13.0	18.5**	2946**	232	289**
111	237	6.3	14.6	135	380**	203
023	239	4.1	21.9**	385**	775**	279**
010	256	12.9	11.5	652**	119	144

TABLE 2-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC OUTPATIENT POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA	CT	Total MC
055	258	6.8	7.5	189	342	185
102	259	10.9	23.9**	1894**	423**	400**
026	260	18.5	20.4**	1949**	295	248**
107	262	13.1	10.1	231	628**	153
038	269	7.6	15.7	222	152	152
140	277	4.0	29.1**	744**	602**	254**
074	278	5.2	24.1**	699**	296	187
002	278	14.6	14.8**	554**	259	277**
019	282	8.5	12.4	329**	262	161
035	287	5.8	9.8	230	390**	218
049	290	3.9	33.0**	140	275	138
078	290	10.9	12.5	197	240	209
045	291	8.7	9.5	162	613**	132
092	294	14.9	19.3**	500**	246	167
137	297	6.8	10.1	631**	340	184
072	298	6.7	19.7**	375**	302	246**
149	310	8.3	16.1	314**	199	149
047	312	4.9	15.9	277**	271	173
060	312	9.4	8.0	100	228	203
046	314	6.5	16.2	142	336	125
093	318	6.4	16.5**	304**	361**	130
014	321	14.5	10.7	275**	233	170
188	327	7.1	17.8**	263	507**	258**
032	340	6.6	8.6	150	133	133
147	347	7.6	18.2**	305**	219	265**
001	351	4.7	20.8**	199	402**	223
090	353	4.9	20.7**	144	419**	178
008	358	5.4	11.6	372**	529**	177
104	360	12.7	12.1	260	89	77
110	370	3.0**	17.1**	456**	297	150
103	371	18.7	14.5	257	219	180
056	373	6.5	12.4	236	415**	189
048	374	3.6**	9.7	167	237	230**
131	377	10.9	13.6	256	220	85
122	378	76	21.9**	906**	227	196
004	385	8.6	10.3	109	288	92
120	390	9.8	22.9**	499**	529**	260**
138	405	6.9	14.7	334**	238	188
141	407	8.1	14.3	168	259	263**
101	408	5.9	9.2	160	134	40
145	410	3.7**	25.4**	567**	550**	349**
027	415	11.1	10.6	169	278	164
028	418	5.6	34.6**	608**	589**	351**
011	420	10.6	18.8**	683**	1014**	282**
081	421	6.6	16.5**	861**	641**	531**
033	423	4.2	16.3**	156	194	170
057	425	18.3	13.5	209	381**	321**
021	427	18.9	12.1	223	524**	168
135	430	8.8	13.5	284**	412**	180
097	435	15.4	10.9	353**	465**	119
052	438	6.8	15.2	281**	372**	236**
132	448	12.6	16.8**	1931**	394**	250**
086	451	12.1	6.6	139	208	107
148	458	13.9	11.4	187	322	238**
012	466	15.3	8.3	560**	250	144
083	466	12.0	13.7	366**	214	193
133	470	13.8	10.8	290**	275	55
017	475	4.0	39.6**	196	467**	220
053	476	13.4	12.3	226	206	125
009	482	6.5	25.3**	240	470**	214
066	498	9.6	12.9	374**	233	92
031	507	11.0	14.8	173	278	220
099	507	10.4	9.6	124	233	63
128	507	4.6	9.4	294**	324	176
013	514	11.3	15.9	168		
151	522	7.8	14.3	370**	324	215
077	523	6.8	17.7**	184	210	214
079	523	15.6	13.0	316**	223	251**
054	524	4.9	10.0	148	230	123
020	524	9.9	14.2	235	366**	190
069	528	7.0	9.7	257	281	83
085	536	4.0	22.5**	97	191	114
084	551	14.2	12.5	166	179	131

TABLE 2-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC OUTPATIENT POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA	CT	Total MC
082	559	12.3	14.6	208	371**	182
117	560	3.4**	18.8**	102	176	88
061	561	12.7	9.8	170	404**	152
006	567	4.6	16.8**	138	688**	165
129	567	4.9	16.2	363**	495**	331**
003	570	11.4	12.9	189	330	230**
115	576	6.3	17.8**	128	231	95
089	578	10.3	12.0	147	258	236**
143	581	2.6**	42.7**	165	555**	208
114	583	5.1	16.6**	599**	660**	177
080	593	9.5	18.0**	208	289	142
015	598	7.0	12.4	167	381**	95
039	598	9.6	18.1**	691**	719**	354**
070	612	5.6	13.7	197	296	82
051	622	12.9	8.3	119	246	150
139	628	8.5	7.8	145	166	83
150	628	8.6	14.5	295**	315	183
043	635	5.9	13.7	239	272	189
096	651	17.4	9.7	326**		
073	657	7.0	9.5	186	238	78
127	665	5.8	8.1	166	344**	147
121	677	10.2	9.5	226	346**	173
034	694	15.9	12.1	406**	592**	584**
124	697	9.7	11.0	63	179	60
123	702	10.4	10.6	186	148	96
113	705	7.6	8.4	107	534**	92
071	709	10.6	11.3	207	584**	141
076	722	8.1	10.5	271	489**	138
044	724	7.3	12.1	212	683**	217
040	731	15.1	7.4	205	149	136
062	741	4.4	18.7**	153	856**	416**
025	741	10.0	12.2	224	344**	121
119	755	5.9	10.1	187	377**	61
075	757	10.0	24.7**	246	345**	276**
098	759	13.8	13.9	380**	239	156
134	769	7.5	10.4	125	131	81
087	773	25.0	10.1	181	285	135
142	788	4.6	12.1	166	273	129
064	792	15.4	8.6	218	299	139
094	793	16.6	10.0	186	179	173
022	808	8.8	14.4	184	271	161
112	812	12.0	9.2	181	184	108
125	817	14.4	11.0	158	242	72
106	862	5.3	9.2	94	300	95
146	890	13.9	11.9	135		
058	897	5.3	18.5**	154	460**	80
063	943	17.8	19.7**	277**	642**	306**
095	960	25.3	10.7	135	181	111
152	963	9.4	8.8	198		
130	971	15.9	13.5	106	307	84
059	1063	9.4	9.7	129	378**	54
105	1109	11.0	6.1	87	155	64
136	1163	6.0	13.1	250	565**	122
065	1251	14.5	10.7	88	147	88
029	1490	22.2	9.7	129	111	105
144	1536	7.0	17.7**	216	694**	418**
068	1809	12.7	10.4	59	128	39

TABLE 3

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC NURSING HOME POPULATION

Patient	B_{12}	Folate	Homocysteine	Methylmalonic Acid
NH170	8**	14.0	34.8**	3365**
NH129	40**	7.4	40.9**	6245**
NH156	44**	22.4	17.4**	1130**
NH139	56**	9.7	20.9**	1180**
NH132	67**	7.6	92.4**	12641**

TABLE 3-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC NURSING HOME POPULATION

Patient	B_{12}	Folate	Homocysteine	Methylmalonic Acid
NH176	129**	9.2	20.3**	1156**
NH196	136**	6.2	41.0**	1077**
NH109	139**	9.8	20.9**	1294**
NH203	146**	4.3	12.2	437**
NH141	161**	13.4	12.2	223
NH178	172**	8.2	5.9	141
NH103	189**	5.5	13.1	362**
NH181	196**	6.3	14.7	296**
NH160	206	11.9	12.5	640**
NH197	221	24.0	10.5	654**
NH073	222	3.6**	19.8**	490**
NH110	227	5.5	13.7	1297**
NH010	228	4.0	21.1**	413**
NH012	234	8.7	16.0	596**
NH037	236	11.5	22.5**	11299**
NH114	238	12.8	13.2	442**
NH211	240	6.0	14.1	166
NH075	250	9.3	12.1	170
NH172	255	7.2	14.4	552**
NH148	259	5.7	19.2**	317**
NH138	264	9.2	16.7**	340**
NH150	264	4.0	13.7	98
NH099	272	5.5	12.5	125
NH124	275	6.9	11.5	87
NH179	301	7.6	7.1	143
NH135	302	6.5	23.4**	397**
NH087	304	7.8	10.8	327**
NH180	304	5.8	10.5	237
NH209	306	7.6	11.9	105
NH107	310	3.3**	8.6	148
NH081	320	4.3	23.6**	470**
NH068	324	7.9	13.4	243
NH183	325	7.7	11.1	144
NH033	330	13.8	7.7	149
NH161	333	8.5	11.3	385**
NH192	337	10.7	9.5	209
NH136	340	6.7	18.2**	409**
NH191	342	20.2	13.4	271
NH137	343	4.0	15.6	183
NH182	346	8.2	14.4	448**
NH020	347	8.4	10.4	149
NH165	351	18.5	11.8	425**
NH095	352	8.5	14.5	366**
NH194	361	4.3	20.3**	305**
NH106	362	4.8	12.9	298**
NH060	367	4.7	16.4**	71
NH009	368	5.1	15.9	325**
NH071	382	4.9	12.9	330**
NH080	390	6.1	15.0	171
NH013	407	6.7	12.4	310**
NH126	409	9.2	17.4**	137
NH030	411	11.2	10.4	844**
NH210	413	8.6	11.9	210
NH158	414	5.7	16.2	508**
NH027	416	10.2	15.5	769**
NH003	424	16.5	9.5	167
NH187	429	4.7	8.8	439**
NH022	430	10.5	14.0	214
NH082	436	10.6	17.7**	340**
NH162	438	6.1	19.2**	180
NH021	439	5.3	15.1	191
NH056	447	11.7	10.9	184
NH119	448	3.2**	14.1	241
NH120	448	5.6	12.0	138
NH186	450	4.7	23.1**	213
NH064	451	6.9	10.6	237
NH057	453	14.6	10.4	282**
NH131	454	8.1	16.2	258
NH059	462	6.0	9.1	147
NH202	465	3.3**	17.0**	393**
NH134	475	15.3	11.6	321**
NH083	475	7.4	10.6	178
NH199	479	15.1	10.4	141
NH042	482	6.0	15.0	141

TABLE 3-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC NURSING HOME POPULATION

Patient	B_{12}	Folate	Homocysteine	Methylmalonic Acid
NH200	491	13.6	9.8	154
NH213	497	8.1	10.0	92
NH143	500	5.2	22.1**	175
NH031	502	6.4	16.1	151
NH188	504	12.5	15.1	1461**
NH171	504	10.7	12.9	344**
NH008	505	4.6	9.9	185
NH102	506	16.6	9.1	236
NH145	512	7.7	22.2**	161
NH093	514	5.1	17.7**	185
NH118	524	25.0	10.1	314**
NH185	524	8.7	12.1	84
NH111	527	5.1	18.4**	250
NH149	530	12.6	18.2**	531**
NH011	534	8.1	12.5	654**
NH128	540	4.3	11.6	120
NH035	547	7.5	9.8	193
NH005	551	17.7	5.0	365**
NH212	552	11.9	12.1	202
NH007	554	6.4	26.1**	646**
NH086	554	9.5	5.1	127
NH069	555	22.7	6.8	134
NH121	555	8.2	10.0	112
NH117	571	6.6	9.7	351**
NH055	581	14.8	9.1	265
NH025	581	5.2	15.3	181
NH104	583	3.9	14.6	1699**
NH173	583	11.2	10.6	160
NH177	584	6.2	5.7	111
NH207	586	8.5	16.4**	243
NH070	591	5.4	12.0	168
NH038	592	8.0	8.8	230
NH049	599	10.7	21.7**	238
NH062	606	4.5	7.7	96
NH153	608	7.7	13.6	221
NH206	611	6.6	16.4**	400**
NH018	614	6.3	10.9	123
NH163	616	5.0	9.6	132
NH189	619	7.6	12.0	158
NH045	620	21.0	12.4	265
NH074	621	10.2	9.2	172
NH054	623	8.0	9.8	121
NH152	625	8.2	7.8	206
NH140	637	21.7	13.6	300**
NH050	642	16.3	13.5	275**
NH089	644	7.7	16.7**	444**
NH036	649	7.9	10.7	68
NH097	651	6.6	13.4	426**
NH016	656	4.1	61.0**	356**
NH053	657	14.2	10.6	320**
NH066	658	7.7	11.4	228
NH051	659	4.0	10.7	216
NH108	671	5.8	24.0**	823**
NH058	673	6.0	11.2	392**
NH028	675	22.3	9.1	105
NH204	678	4.7	10.2	148
NH169	679	6.9	19.2**	267
NH032	681	12.7	5.9	99
NH065	682	11.0	13.5	176
NH061	683	13.4	9.6	190
NH116	685	9.0	7.5	244
NH015	699	6.8	16.8**	236
NH157	711	10.0	12.8	198
NH155	715	10.0	17.6**	308**
NH034	715	7.9	11.4	179
NH040	717	10.5	15.7	256
NH105	718	6.0	13.2	308**
NH048	719	8.0	10.8	207
NH084	720	6.8	9.4	169
NH115	724	16.3	9.4	161
NH205	734	8.5	13.3	232
NH113	738	11.7	10.3	171
NH154	738	13.7	9.6	123
NH167	741	17.0	6.6	129

TABLE 3-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC NURSING HOME POPULATION

Patient	B_{12}	Folate	Homocysteine	Methylmalonic Acid
NH190	752	5.2	14.1	254
NH067	760	22.5	9.5	232
NH014	767	8.9	7.3	100
NH072	768	8.3	6.9	131
NH133	772	8.8	20.4**	219
NH122	778	6.0	10.4	108
NH076	781	12.1	14.9	282**
NH147	785	7.5	24.5**	411**
NH026	786	9.7	8.3	146
NH151	789	24.4	11.1	182
NH198	797	10.9	10.7	158
NH088	801	6.4	18.3**	184
NH004	806	11.3	8.8	96
NH024	818	5.1	14.1	219
NH100	826	16.4	10.5	103
NH078	831	7.2	10.3	266
NH052	844	19.6	8.0	193
NH142	848	18.6	12.1	398**
NH002	862	9.4	11.3	212
NH091	891	4.9	12.6	169
NH127	897	22.0	8.4	132
NH096	901	9.3	5.2	104
NH201	910	25.0	15.7	424**
NH184	941	21.5	10.8	170
NH208	945	20.2	9.8	111
NH130	968	22.4	10.4	339**
NH164	989	8.0	16.8**	102
NH077	1006	15.1	9.2	188
NH017	1015	11.9	9.5	175
NH029	1053	18.6	11.4	161
NH023	1055	9.3	9.7	193
NH047	1079	6.4	11.4	106
NH043	1082	14.5	13.9	144
NH195	1088	36.9	12.2	150
NH193	1092	8.2	15.7	225
NH046	1093	9.2	18.8**	186
NH101	1108	3.9	8.1	139
NH098	1117	11.3	12.3	88
NH168	1124	25.2	15.0	203
NH006	1126	6.9	8.1	159
NH144	1135	8.0	21.9**	262
NH044	1159	26.8	10.2	109
NH175	1162	7.8	12.0	210
NH146	1179	9.8	10.1	129
NH112	1238	10.3	15.0	347**
NH001	1304	13.1	6.9	142
NH166	1337	13.4	8.3	67
NH079	1346	18.0	12.0	248
NH041	1528	20.7	8.2	155
NH063	1559	15.0	7.0	66
NH159	1566	6.6	15.5	451**
NH125	1703	8.2	20.6**	153
NH094	1768	15.9	8.4	182
NH123	2028	10.2	16.8**	286
NH174	2106	13.3	12.8	280**
NH039	2227	23.8	8.9	119
NH019	2297	11.1	15.5	177
NH092	2360	5.7	9.8	131
NH085	3141	22.0	26.9**	1947**

TABLE 4

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA
495	77**	10.0	65.4**	3145**
484	84**	10.0	77.5**	6820**
522	100**	3.6**	15.5	967**
455	115**	1.9**	21.8**	170

TABLE 4-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA
493	135**	4.4	16.9**	421**
528	145**	3.9	38.3**	729**
510	155**	4.6	14.1	804**
502	155**	2.1**	16.9**	347**
412	160**	18.5**	33.8**	1301**
409	160**	4.8	16.8**	164
470	165**	9.2	19.9**	1468**
460	165**	6.8	11.5	142
437	170**	4.9	16.5**	813
439	170**	1.2**	21.3**	502**
525	175**	11.5	15.3	1058**
442	175**	4.2	17.5**	328**
456	180**	7.3	11.1	206
450	180**	5.0	11.8	196
477	185**	3.4**	31.4**	369**
508	190**	4.1	19.5**	335**
423	190**	2.5**	19.0**	329**
462	190**	3.8	11.6	276**
523	190**	5.6	16.8**	207
482	190**	2.9**	25.1**	179
459	190**	5.3	19.6**	167
543	195**	4.3	13.5	470**
520	195**	1.7**	22.2**	309**
431	195**	7.2	13.5	251
513	200	5.0	25.0**	1184**
534	200	4.9	32.6**	1080**
515	200	4.9	17.3**	478**
531	200	5.1	26.8**	466**
516	200	3.6**	17.8**	279**
526	200	1.6**	23.5**	171
471	205	5.7	22.0**	542**
413	205	2.6**	20.4**	304**
497	205	3.3**	19.4**	258
539	205	4.1	15.4	247
544	205	12.5	11.7	233
540	205	4.0	17.1**	185
517	205	2.2**	15.0	151
496	210	3.7**	15.2	1103**
488	210	16.5	21.8**	600**
416	215	12.5	10.0	197
434	220	7.1	24.8**	430**
545	220	11.5	14.4	407**
547	220	5.3	17.5**	396**
408	220	3.2**	16.4**	357**
449	220	3.7**	13.7	272**
507	220	8.5	10.0	179
458	225	10.5	21.1**	964**
491	225	7.2	16.0	472**
529	230	2.0**	61.1	1172**
415	230	3.2**	28.9**	377**
453	230	3.6**	19.8**	336**
448	230	5.2	13.1	319**
498	230	5.9	20.1**	255
533	230	5.7	11.7	151
466	235	35.0	12.1	617**
537	235	5.7	10.7	394**
483	235	8.6	16.6**	344**
512	235	3.9	12.5	190
452	240	4.7	26.5**	1068**
454	240	5.2	11.9	201
535	240	4.4	15.3	195
421	245	10.5	12.5	464**
469	245	6.2	20.0**	448**
474	245	7.3	10.3	327**
486	245	9.2	12.6	156
536	250	22.5	20.3**	1068**
475	250	5.6	23.0	456**
511	250	2.7**	23.1**	398**
465	250	4.1	23.1**	323**
506	250	5.2	11.5	252
417	250	5.5	25.2**	241
524	1250	2.5**	14.4	212
411	250	9.9	11.5	200
492	250	5.2	10.7	182

TABLE 4-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA
548	250	2.9**	12.4	179
441	250	4.5	8.5	147
480	255	4.8	16.9**	558**
532	255	7.0	14.8	419**
464	255	11.5	12.9	400**
494	255	6.2	12.1	293**
106	255	4.5	11.7	203
546	260	5.5	14.7	662**
541	260	5.4	30.8**	426**
420	260	5.3	13.6	347**
500	260	6.7	14.0	330**
538	260	9.3	17.3**	298**
457	260	2.9**	12.6	286**
472	260	8.3	13.8	278**
424	260	8.3	10.1	242
433	260	6.8	10.5	197
425	265	7.3	14.7	724**
468	265	3.8	16.7**	289**
435	265	7.4	14.0	150
499	265	2.2**	12.4	131
432	270	4.3	28.3**	432**
521	270	3.7**	15.3	349**
549	270	4.21	12.4	343**
518	270	10.0	10.1	276**
418	270	26.0	9.4	213
419	270	6.5	12.5	212
428	270	4.2	18.7**	189
443	270	8.8	12.0	187
446	270	11.0	8.1	157
461	275	7.6	15.1	663**
440	275	4.9	12.9	248
436	275	6.3	30.1**	233
530	275	7.4	13.6	231
438	275	4.6	8.5	221
527	275	7.5	10.5	219
444	275	4.0	12.2	180
429	280	5.3	15.3	463**
503	280	4.4	25.7**	421**
485	280	3.5**	15.6	381**
410	280	14.5	10.0	201
487	280	3.9	10.5	166
430	280	9.2	8.8	161
519	285	3.9	22.2**	919**
476	285	10.5	12.8	339**
509	285	5.4	13.0	331**
501	285	5.5	12.4	252
542	285	6.9	15.5	242
445	285	7.2	14.9	237
427	285	4.0	17.1**	233
490	290	4.7	13.9	203
451	290	2.1**	20.0**	226
414	290	7.0	9.7	117
467	290	4.1	6.5	68
463	295	5.8	12.3	296**
473	295	7.5	14.4	290**
505	295	4.1	12.4	257
198	300	11.5	10.9	323**
195	300	9.8	12.2	216
207	305	7.7	13.2	330**
67	305	8.6	15.4	312**
50	305	9.0	11.6	235
70	305	12.5	12.7	228
113	305	5.6	13.5	201
39	305	6.9	19.7**	170
3	305	4.2	11.5	135
325	305	14.5	9.4	94
368	310	4.7	15.9	371**
322	310	7.8	15.3	362**
295	310	7.2	13.8	305**
347	310	5.8	16.5**	266
313	310	6.1	16.5**	219
355	310	5.5	15.4	138
291	310	4.5	15.2	125
478	315	23.0	17.7**	857**

TABLE 4-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA
53	315	5.8	12.1	505**
240	315	6.7	12.3	394**
14	315	9.6	14.2	331**
137	315	7.8	24.3**	306**
254	315	8.7	17.0**	285**
109	315	3.7**	16.5**	263
252	315	5.2	10.1	241
186	315	4.1	15.4	238
183	315	5.5	10.7	195
390	315	6.9	10.0	188
267	315	2.2**	12.0	124
310	320	12.0	13.8	395**
31	320	17.0	12.9	334**
88	320	4.8	13.8	217
403	320	9.6	11.3	162
60	320	6.2	11.4	155
315	320	6.4	9.9	136
175	325	6.3	17.8**	486**
317	325	22.0	14.0	294**
18	325	6.3	11.3	241
247	325	13.5	13.2	231
223	325	9.2	12.6	203
132	325	3.7**	15.4	184
168	325	4.3	10.2	174
238	325	5.5	9.9	166
117	325	5.2	15.0	154
404	330	2.5**	33.1**	1085**
138	330	4.8	11.3	360**
316	330	3.6**	10.2	272**
61	330	5.1	12.5	242
333	330	34.0	9.2	235
16	330	4.6	13.3	211
276	330	5.7	11.9	200
391	330	4.1	8.4	184
362	330	9.2	11.7	178
1	330	9.9	8.9	170
379	335	16.0	12.1	471**
147	335	9.0	9.7	427**
89	335	8.0	15.3	385**
211	335	5.0	12.2	374**
45	335	5.9	16.3**	250
47	335	5.0	13.6	249
402	335	4.7	13.5	230
314	335	7.6	9.7	203
150	335	4.8	11.2	119
120	340	1.9**	21.0**	775**
284	340	7.2	25.6**	439**
230	340	14.0	11.4	419**
149	340	8.8	18.9**	337**
269	340	3.9	16.2	302**
197	340	10.5	12.8	233
19	340	9.6	11.0	232
422	340	3.1**	14.4	188
196	340	11.5	8.9	169
40	345	8.7	14.6	610**
244	345	8.6	15.8	461**
287	345	5.7	18.1**	427**
100	345	8.3	14.8	403**
383	345	4.3	27.2**	284**
62	345	19.5	9.6	250
350	345	8.0	10.0	249
65	345	8.0	10.2	247
307	345	16.5	11.6	208
69	345	17.0	9.9	197
328	345	7.5	8.9	192
43	345	6.0	13.2	191
222	345	6.1	9.2	175
306	345	4.3	17.2**	160
154	345	7.1	10.2	148
94	350	4.8	16.1	302**
201	350	6.1	9.9	200
13	350	5.1	10.9	193
236	355	7.2	14.8	309**
191	355	5.8	15.3	257

TABLE 4-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA
481	355	5.2	17.1**	134
92	360	4.2	25.2**	321**
324	360	3.8	16.6**	264
87	360	3.3**	13.3	200
46	360	5.4	11.1	179
289	360	9.5	7.9	129
392	360	5.1	10.3	125
320	365	6.4	17.3**	240
134	365	13.5	11.8	238
239	365	7.7	13.2	236
326	365	6.0	10.9	180
364	365	4.1	13.9	154
218	365	7.5	11.2	126
216	365	6.2	12.2	119
248	365	5.7	13.3	117
375	370	4.1	20.7**	532**
288	370	6.4	18.8**	436**
161	370	6.3	11.2	340**
244	370	19.5	9.8	286**
330	370	18.0	12.2	228
334	370	12.5	8.7	172
275	370	6.9	12.7	162
54	375	7.3	10.1	583**
185	375	9.3	10.5	386**
52	375	8.1	15.5	291**
366	375	5.0	12.5	280**
93	375	3.3**	16.2	248
151	375	2.9**	12.3	235
85	375	6.7	14.8	217
294	375	7.0	12.2	184
361	375	7.9	10.7	179
318	375	5.5	13.7	160
386	375	7.6	10.4	153
304	375	9.1	9.4	132
228	380	7.7	17.1**	320**
110	380	4.0	7.2	135
204	380	5.7	10.6	91
348	385	2.3**	17.4**	368**
146	385	11.5	12.5	253
260	385	5.5	13.7	211
136	385	3.6**	19.8**	205
338	385	5.0	16.2	180
376	385	3.6**	13.7	154
194	385	12.5	7.9	153
504	385	38.0	9.5	138
160	390	8.1	24.7**	475**
354	390	11.5	12.8	212
25	390	5.1	11.3	205
387	390	8.7	8.4	162
86	390	21.0	12.6	133
133	390	3.9	11.3	113
331	395	12.0	20.1**	638**
130	395	10.5	10.8	256
82	395	2.8**	9.8	236
119	395	12.5	16.3**	209
380	395	10.5	14.3	159
373	395	5.5	11.6	152
256	395	10.5	9.9	149
384	395	7.3	14.7	116
105	400	19.0	10.5	322**
251	400	4.8	14.9	289**
392	400	11.5	9.6	181
279	400	4.5	11.7	170
339	400	7.4	13.6	168
381	405	6.7	12.4	294**
285	405	7.0	14.2	281**
340	405	3.6**	19.6**	275**
51	405	6.5	14.3	233
33	405	6.5	9.6	207
268	405	3.3**	14.9	205
73	405	5.2	13.1	172
17	410	7.5	16.2	473**
286	410	4.7	18.8**	415**
140	410	5.9	21.7**	302**

TABLE 4-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA
116	410	6.8	14.5	218
396	410	5.6	16.1	190
356	410	1.9**	27.6**	149
237	410	3.6**	16.6**	122
112	410	5.5	8.9	107
259	410	4.7	11.6	99
176	415	5.2	21.9**	453**
193	415	10.5	11.3	163
323	415	6.1	9.6	163
202	415	11.5	9.4	150
398	415	8.0	12.6	134
321	420	5.2	10.7	383**
142	420	29.0	8.3	234
327	420	3.2**	14.6	203
342	420	7.3	9.4	156
170	420	20.5	10.3	142
345	420	29.5	13.2	136
302	420	8.6	8.8	128
115	425	6.3	22.2**	628**
97	425	12.5	19.8**	313**
246	425	8.7	15.1	241
72	425	10.5	13.5	241
365	425	6.7	16.7**	237
139	425	12.5	10.4	224
143	425	8.1	13.5	216
426	425	19.5	14.5	201
303	425	3.0**	14.5	154
388	425	6.2	12.3	135
127	425	6.7	8.4	100
262	430	10.0	12.1	323**
270	430	4.8	12.9	293**
514	430	4.3	12.9	197
341	430	3.5**	19.9**	190
278	430	5.2	10.8	182
370	430	11.0	15.3	174
55	430	7.6	11.0	162
274	430	5.0	8.2	131
367	430	17.5	8.0	126
98	430	13.5	12.8	125
337	435	13.5	14.1	395**
309	435	8.7	12.9	349**
305	435	17.5	15.4	187
144	435	25.0	8.9	167
34	435	8.6	7.6	157
234	435	9.7	9.2	116
123	440	9.6	12.2	622**
200	440	4.8	12.4	257
250	440	7.5	12.9	248
107	440	6.3	14.7	183
300	440	6.5	7.9	123
374	445	5.4	14.0	247
372	445	11.0	11.0	181
36	445	4.0	10.0	181
271	445	7.2	10.4	124
242	445	15.5	9.6	112
264	445	6.0	10.7	100
172	450	11.5	14.9	607**
32	450	11.5	13.6	362**
346	450	13.5	15.8	330**
41	450	8.5	11.4	194
95	450	5.1	12.5	182
357	455	6.3	14.4	296**
319	455	17.0	10.2	147
308	455	15.0	9.8	131
235	455	23.0	9.0	124
349	455	9.2	8.3	82
178	460	5.6	20.6**	473**
312	460	4.7	14.4	197
79	460	5.0	10.4	173
131	460	18.0	10.2	162
243	460	2.6**	11.6	160
261	465	7.7	10.6	252
378	465	5.4	13.2	221
49	465	47.0	10.8	179
226	465	7.7	10.2	173
377	465	5.6	8.5	143
253	465	10.0	7.0	138
76	470	12.5	14.8	304**
203	470	15.0	7.6	233
296	470	23.5	11.0	161
382	470	5.3	11.1	109
6	475	10.5	12.5	232
75	475	4.5	8.1	150
332	475	9.4	10.0	144
290	475	14.0	9.1	143
128	475	5.9	9.3	133
124	475	6.0	13.5	111
177	475	8.8	9.1	106
126	480	11.0	11.0	212
283	480	5.2	10.6	175
209	480	10.5	10.5	175
293	480	6.8	15.5	135
121	485	4.7	20.0**	345**
282	485	12.0	10.9	236
71	485	13.5	8.1	168
385	485	9.0	14.1	128
190	495	9.9	10.4	410**
210	495	8.6	12.0	243
155	495	5.9	10.4	219
336	495	13.5	9.9	135
280	500	8.7	14.5	334**
96	500	4.7	10.8	237
145	500	5.9	17.5**	233
199	500	4.2	13.8	199
489	500	11.5	9.7	198
217	500	6.4	9.6	166
90	500	7.5	8.5	106
164	510	5.2	23.8**	408**
343	510	4.5	13.7	284**
42	510	4.9	7.4	233
351	510	8.5	11.0	207
299	510	12.0	8.0	104
99	520	10.5	25.8**	322**
114	520	30.0	10.9	220
369	520	29.0	16.7**	206
37	520	10.5	8.6	191
251	520	6.7	16.8**	151
403	520	7.5	12.6	148
229	520	7.9	11.0	116
135	520	3.2**	8.3	88
81	530	6.8	14.8	372**
91	530	14.5	10.6	228
167	530	23.5	9.2	176
181	530	5.5	9.3	171
56	530	20.0	8.3	163
5	530	13.5	8.1	159
180	540	12.0	9.0	216
311	540	4.1	13.3	214
389	540	3.9	13.9	169
125	540	5.5	13.0	159
35	540	22.5	11.0	123
104	550	10.5	16.5**	544**
393	550	4.9	11.9	339**
394	550	23.0	14.0	278**
292	550	6.9	16.2	263
163	550	6.7	14.3	219
66	550	10.5	11.6	206
29	550	17.5	9.6	191
227	550	7.9	11.7	154
38	550	7.5	11.9	152
241	550	10.5	9.8	100
102	550	9.7	8.6	91
77	560	24.0	14.8	554**
162	560	10.5	11.8	275**
273	560	8.7	9.4	180
80	560	6.3	11.2	108
255	560	8.8	9.9	93
122	570	66.0	13.8	304**

TABLE 4-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA
208	570	34.0	10.2	255
23	570	21.5	8.3	241
447	570	25.0	10.0	164
225	570	5.7	12.2	154
174	570	7.1	11.8	127
11	570	19.0	8.9	113
165	580	10.5	14.8	226
182	580	8.9	8.2	189
245	590	15.5	10.8	262
83	590	17.5	8.3	199
166	590	11.5	9.4	188
158	590	7.3	10.7	166
187	590	4.5	11.0	146
156	590	23.5	11.3	112
231	600	9.5	9.0	192
78	600	11.5	9.4	151
329	610	15.0	7.3	312**
57	610	16.0	11.9	286**
7	610	12.0	10.4	195
277	610	9.5	7.8	153
108	620	13.5	8.4	191
205	620	18.0	7.5	145
263	620	9.8	10.2	101
9	630	4.9	11.4	300**
111	630	8.3	11.1	276**
68	630	11.5	8.9	143
399	630	14.0	11.0	90
266	640	5.1	15.7	364**
12	640	24.5	9.0	233
152	640	8.1	10.0	209
405	640	7.0	12.8	186
27	640	22.5	8.4	136
258	640	8.3	11.2	120
249	640	8.7	9.1	81
297	650	16.0	10.0	279**
192	650	4.9	14.9	213
257	650	3.3**	16.3**	208
184	650	12.5	9.9	193
58	650	18.5	10.7	172
301	650	16.0	15.5	162
397	650	12.5	8.4	146
272	650	11.0	7.4	120
153	650	7.1	13.1	116
406	650	6.6	5.8	81
10	660	9.0	7.6	154
26	660	22.0	8.3	132
265	670	3.9	19.3**	509**
359	670	21.0	8.3	269
48	670	32.0	9.9	262
335	670	11.5	8.1	121
189	680	6.6	17.9**	358**
220	680	15.5	10.9	115
15	690	13.5	13.4	159
44	700	20.0	12.7	244
21	700	13.5	10.2	129
74	700	15.0	7.1	65
4	710	29.0	8.5	266
353	710	11.5	11.4	206
281	710	10.5	9.6	185
2	710	8.0	8.5	109
212	740	20.0	11.1	250
8	740	12.0	11.5	216
206	750	12.5	8.3	116
101	770	14.5	12.7	372**
344	770	32.0	11.7	297**
20	770	35.0	10.1	245
407	770	10.5	12.0	110
360	780	2.7**	20.9**	157

TABLE 4-continued

SERUM METABOLITE & VITAMIN LEVELS IN A GERIATRIC POPULATION

Patient	B_{12}	Folate	Homocysteine	MMA
232	790	15.5	10.1	151
141	790	12.5	9.5	74
129	800	8.7	11.7	211
188	800	15.0	12.3	174
400	800	12.5	10.3	156
24	810	23.0	7.5	194
173	830	35.0	11.4	243
214	830	21.5	12.0	187
63	830	13.8	8.8	185
148	830	45.0	7.1	146
84	830	23.5	7.0	136
179	830	16.5	6.6	96
171	840	23.5	11.2	195
28	870	5.8	15.9	197
233	870	7.9	12.7	169
221	870	40.0	7.0	126
371	880	20.0	8.5	152
213	890	10.5	18.0**	231
358	900	21.0	8.3	149
296	910	15.5	10.2	221
118	910	100.0	9.7	170
479	950	11.5	12.1	188
30	950	6.2	10.5	170
159	1000	9.5	8.7	281**
219	1050	37.0	14.3	313**
103	1050	12.5	10.3	154
59	1150	17.5	7.3	180
157	1250	12.0	14.9	206
363	1350	28.0	10.4	190
22	1400	13.5	10.4	233
64	1400	31.0	9.7	149
169	1450	15.0	9.5	150

What is claimed is:

1. An oral vitamin formulation comprising approximately 2.0 mg vitamin B_{12} and 0.4 mg folic acid.

2. The formulation of claim 1, further comprising 5–75 mg vitamin B_6.

3. The formulation of claim 2, having approximately 25 mg vitamin B_6.

4. An oral vitamin formulation, comprising approximately 2 mg vitamin B_{12} and 1.0 mg folic acid.

5. The formulation of claim 4, further comprising 5–75 mg vitamin B_6.

6. The formulation of claim 5, having approximately 25 mg vitamin B_6.

7. An oral vitamin formulation comprising approximately 2.0 mg vitamin B_{12} and 0.1–0.4 mg folic acid.

8. The formulation of claim 7, further comprising 5–75 mg vitamin B_6.

9. The formulation of claim 8, having approximately 25 mg vitamin B_6.

10. An oral vitamin formulation, comprising approximately 2 mg vitamin B_{12}, 0.4–10.0 mg folic acid, and further comprising 5–75 mg vitamin B_6.

11. The formulation of claim 10, having approximately 25 mg vitamin B_6.

* * * * *